Dichotomic classification of sensory neurons: Elegant but problematic

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B-Afferents: A fundamental division of the nervous system mediating homeostasis?

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Abstract: The peripheral nervous system (PNS) has classically been separated into a somatic division composed of both afferent and efferent pathways and an autonomic division containing only efferents. J. N. Langley, who codified this asymmetrical plan at the beginning of the twentieth century, considered different afferents, including visceral ones, as candidates for inclusion in his concept of the "autonomic nervous system" (ANS), but he finally excluded all candidates for lack of any distinguishing histological markers. Langley's classification has been enormously influential in shaping modern ideas about both the structure and the function of the PNS. We survey recent information about the PNS and argue that many of the sensory neurons designated as "visceral" and "somatic" are in fact part of a histologically distinct group of afferents concerned primarily autonomic function. These afferents have traditionally been known as "small dark" neurons or B-neurons. In this target article we outline an association between autonomic and B-neurons based on ontogeny, cell phenotype, and functional relations, grouping them together as part of a common reflex system involved in homeostasis. This more parsimonious classification of the PNS, made possible by the identification of a group of afferents associated primarily with the ANS, avoids a number of confusions produced by the classical orientation. It may also have practical implications for an understanding of nociception, homeostatic reflexes, and the evolution of the nervous system.

Keywords: autonomic; capsaicin; dorsal root ganglion; nerve growth actor; neuroimmunology; nociception; sensory neurons; substance P; sympathetics; tachykinins; visceral afferents

1. Introduction

All of neuroscience uses the fundamental classification that distinguishes the central and peripheral nervous systems – the CNS and PNS, respectively – and classifies the elements of the PNS into subdivisions on the basis of three dichotomies: afferent and efferent, skeletal and autonomic, and somatic and visceral. Given the paradigmatic importance of such a taxonomy, it is noteworthy that neither this accepted systematics nor the resulting assignments have been rigorously reconsidered since the beginning of the twentieth century, when they were considered tentative. In this target article, we suggest that the categorization of PNS afferents, including a description of their relation to the autonomic nervous system (ANS), should be revised to reflect new information about morphology, histochemistry, ontogeny, and function.

As J. N. Langley developed his autonomic nervous system concept, he carefully considered the possibility that there was a specific class of afferents that also belonged to this division of the nervous system. In 1903, after having reviewed a number of possible criteria for classifying afferents, Langley (1903, p. 25) tentatively concluded that autonomic afferents were those fibers "which give rise to reflexes in autonomic tissues, and which are incapable of directly giving rise to sensation." He was reluctant to classify afferents according to functional criteria, however, and hoped to rely eventually on morphological criteria. At the end of his 1903 paper he wrote: "Further progress awaits the discovery of some distinguishing histological character [i.e., marker of autonomic afferents]."

Eighteen years later, in his book, *The Autonomic Nervous System, Part I* (1921), Langley excluded once and for all the possibility of autonomic afferents (see Figure 1). Although he planned (Langley 1921, p. 9) to reexamine this conclusion in a later publication, the sequel to his 1921 work never appeared, and his "efferents only" version of the ANS has been a source of continuing controversy.

A number of neuroscientists, including authors of major treatises on the ANS (Gabella 1976; Mitchell 1953; Pick 1970), have expressed dissatisfaction with the "efferents only" concept. Nevertheless, it is commonly accepted in textbooks and in the general literature. Even grant proposals have been criticized for suggesting that specific afferents are associated with the ANS (see Norgren 1985). Recently, some investigators have broken with tradition and used terms such as "sympathetic afferents" (Foreman et al. 1986; Malliani 1982; Malliani et al. 1973; Morgan et al. 1986) and "parasympathetic af-

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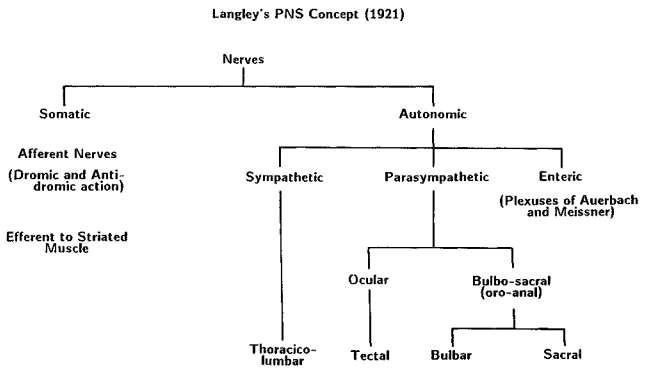


Figure 1. Langley's (1921, p. 10) classification of the peripheral nervous system. Note that all afferents are classified as "somatic," including those with antidromic actions.

ferents" (Kawatani et al. 1985; Mei 1985). Such designators have important uses and in some cases have satisfied specific needs of specialists. It is uncertain whether they are sufficiently cogent to gain general acceptance, however (see section 2.3). To date at least, none of these terms has stimulated a reformulation in the general literature.

A common justification for such designators has been that the afferents in question are found in the nerves, which are labeled "sympathetic" or "parasympathetic." Langley was aware of the existence of afferents in autonomic nerves but he did not regard this as a sufficient reason for invoking another autonomic neuron category. He did not consider the ANS concept an invention for heuristic convenience, but rather a discovery that could be objectively repeated. Earlier, Gaskell (1886, p. 2) had asserted that the test of a "real" fundamental division of the nervous system was whether the proposed functional differences were "bound up with morphological differences." This approach had enabled Gaskell (1886) to delineate the bulbar, thoracolumbar, and sacral visceral nervous outflows and to achieve a revolutionary simplification of the nineteenth-century neuroanatomy. The morphological difference that Gaskell used was the conspicuously small size of myelinated preganglionic autonomic fibers. In a similar fashion, Langley identified "somatic" efferents by their association with multinuclear striated muscle; later he turned to pharmacological criteria in order to distinguish sympathetic and parasympathetic divisions. Such distinctive neuronal traits or markers were considered to reflect distinct ontogenetic histories. In effect, Langley's attempt at systemization was really intended to be not just a special-purpose classification, but a "natural" grouping, analogous to the groupings of some taxonomists (see Mayr 1982). It is in the same spirit of "natural" taxonomy that we readdress the issue of PNS classification.

For more than 100 years, morphologists have contrasted two cell types in the dorsal root ganglia (see Scharf 1958): A-neurons and B-neurons (section 3). In the past decade this A-B neuron typology has been reintroduced, particularly by histochemists and pharmacologists, in a series of papers that has radically revised our thinking about sensory neurons (see Hökfelt et al. 1976; Jancsó et al. 1977). Furthermore, many of the groups of dorsal root ganglion (DRG) neurons that have been distinguished (histochemically or pharmacologically) have characteristics that seriously challenge the validity of current classification systems. For example, substance P-containing afferents, a subpopulation of B-neurons (section 3), not only mediate autonomic functions but have key ontogenetic and phenotypic traits similar to those of autonomic motor neurons. Nevertheless, according to Langley's classification (Figure 1), these neurons would be, and indeed traditionally have been, lumped together with all other spinal afferents. Alternatively, they are fragmented into "general somatic" and "general visceral" categories by the *doctrine of nerve components* (Herrick 1903; 1927).

In this target article we analyze the inadequacies of the current classification systems and propose an alternative, more parsimonious ordering. Our two main hypotheses are: (1) B-neurons represent a major division of the PNS, more fundamental than the traditional categories of "visceral" and "somatic." (2) The ANS is the motor system most closely related to the B-neuron division. In one sense, the B-neurons characterized here represent the afferent division that Langley had searched for, but provisionally ruled out.

2. Classification of nerves and neurons

The current terminology and concepts can be put in perspective by identifying their roots in some of the more influential contributions to PNS classification and to the idea of homeostasis.

The distinctiveness of visceral function must first have been recognized when these inner parts were found to move of their own accord, usually without the knowledge of their owner. In the seventeenth century, such observations led to the idea of involuntary nervous function, introduced to the study of functional anatomy by Thomas Willis (Sheehan 1936). According to Willis (1664, 1965), the cerebrum mediated volition via the flow of animal spirits through the spinal cord and the cerebellum mediated involuntary functions through the vagal and intercostal (sympathetic chain) nerves. The *cerebrospinal system* came to be viewed as the main substrate of volition and sensation. Willis concluded that only the very strong volitions could pass through the cerebellum to the involuntary nerves and thereby modify semivoluntary functions such as breathing. Similarly, he considered mild visceral reactions to be insensible because they were blocked from the cerebrum by the cerebellum. Though few neuroscientists today would consider using volition as a criterion for classifying nerves, most of the autonomic or *vegetative* nervous system concepts, from Willis' time to the present, have been based partly on notions that can be traced to presuppositions about consciousness or volition. Gaskell (1916) went so far as to call this division the "involuntary nervous system."

The forerunner of modern autonomic-somatic concepts was suggested by Xavier Bichat (1827/1977). Bichat divided the life of an organism into an organic mode, controlled by the ganglionic system (autonomic ganglia and plexuses), and an animal mode, mediated by the cerebrospinal system. The function of organic life was nutrition; that of animal life, coordination of relations with the external environment. Whereas the organic

mode was passive and stationary, consisting of a continuous rhythm of assimilation and excretion, the animal mode consisted of variable and episodic behaviors such as locomotion, manipulation, and communication.

Bichat's functional neuroanatomy also had a morphological basis:

> What anatomist, in fact, has not been struck with the differences that exist between the nerves of these two systems? Those of the brain [cerebrospinal or somatic] are larger, less numerous, whiter, more compact in texture and exhibit less variety. On the contrary, the extreme tenuity, great number, especially towards the plexuses, greyish colour, remarkable softness and varieties extremely common are characters of the nerves coming from the ganglions [autonomic] if we except those of communication with the cerebral nerves [communicating rami] and some of those which unite together these small nervous centers. (Bichat 1977, p. 72)

Unfortunately, Bichat underestimated the significance of the white communicating rami and promoted the idea of a decentralized, completely independent, ganglionic (autonomic) nervous system.

Shortly after Bichat's career was ended by his death at the age of 31, Charles Bell (1811, 1966) introduced the idea of specific nerve components. According to Bell, nerves were capable of different functions because they had distinct components with distinct central connections. Previous anatomists had divided the nervous system according to the presumed specializations of *entire* nerves. Bell implied that classification should not be based on nerves, which have a mixture of functional components, but on the parcels of central organization (e.g., nuclei, laminae), "That the nerves of sense, the nerves of motion, and the vital [autonomic] nerves, are distinct through their whole course, though they seem sometimes united in one bundle; and that they depend for their attributes on the organs of the brain to which they are severally attached" (Bell 1966, p. 274). In Bell's time, the same neural element was thought to be able to transmit both different sensations (modalities) and the power of motion.

Three-quarters of a century later, the osmium nerve fiber stain was introduced by Schultz (see Sheehan, 1936) and the power of Bell's idea was realized in the morphological analyses of Gaskell (1886). Gaskell discovered that "real" (1886, p. 2) functional components of the nervous system were correlated not only with distinctive features of central organization but also with morphological traits such as specific fiber size. Gaskell accordingly discriminated the bulbar, thoracolumbar, and sacral autonomic outflows from the somatic fiber components and thereby laid the foundation for the PNS classification systems that prevail today: the doctrine of nerve components and the autonomic nervous system.

2.1. Doctrine of nerve components. According to Herrick (1903), the purpose of the doctrine of nerve components was to divide the PNS into units that had both functional and structural significance. The main idea of the doctrine was that different functional nerve components could be defined by the similarities of their central and peripheral terminal projections. In the case of sensory components, however, it was seldom possible to analyze peripheral terminal/receptor specializations, so peripheral pathways were used as the discriminating criteria instead. The most fundamental division of functions and nerve components was thought to be reflected in the distinction between the visceral responses to internal stimuli and the bodily or somatic responses to external stimuli (Herrick 1903). The inward distribution of innervation was accordingly assumed to correspond to a "visceral" type of function; the outward distribution innervation corresponded to a "somatic" type.

At the turn of the century, these notions of inner/outer functional divisions were validated by their correspondence with discrete features of CNS organization (see Figure 2a). In later years, however, the doctrine was applied according to the pathway of the peripheral processes: Fibers which coursed in visceral nerves, and thus extended inward, were designated "visceral"; fibers of the cerebrospinal nerves were classified as "somatic."

In the case of afferents, recent results do not bear out the doctrine's purported correlation between central organization and peripheral nerve pathway. Although the central terminals of spinal cord afferents do indicate a dichotomous organization, this seems to be related more to fiber type than to inner or outer functions or nerve pathway. In general, the large myelinated afferents terminate in the deep layers of the dorsal horn (especially laminae III & IV); the smaller, unmyelinated, and A-delta fibers terminate predominantly in the superficial layers (laminae I and II; see Figure 2b). Although the fibers of the large myelinated afferents are found mostly, if not exclusively, in somatic nerves that innervate the outer tissues (e.g., skin, muscles, joints), the distal processes of the smaller and unmyelinated afferents are found in all nerve types, passing both to inner and outer tissues. Moreover, some of these unmyelinated afferents have dichotomizing collaterals that pass through both visceral and somatic nerves (Bahr et al. 1981; see neuron labeled "viscero-cutaneous" in Figure 4). In conclusion, there seem to be no compelling reasons for classifying afferents on the basis of gross innervation territories (inner/outer) or the pathways they take.

2.2. Langley's search for autonomic afferents. As discussed in the Introduction, Langley searched for morphological distinctions that would define the afferents falling under his ANS concept, and when he could find none, he declared the ANS to be a purely motor system. This conclusion resulted partly because the fiber stain available to Langley (osmium) would not reveal the majority of visceral afferents, which were unmyelinated (see Langley 1922). When he compared visceral and somatic afferents, he compared the exceptional splanchnic A-beta fibers (myelinated), which innervate mesenteric Pacinian corpuscles (cat), with the more common myelinated fibers of the somatic nerves; of course, they were alike.

Apart from the technical limitations of his day, however, Langley's search was also hampered by the prevailing preconceptions. From the beginning, Langley considered the spinal ganglia and nerves as the anatomical territory of the "somatic" nervous system. Only after he failed to find sensory neurons in the sympathetic ganglia (Langley 1903) did he look to the dorsal root ganglia. Langley would accordingly consider an afferent as autonomic only if at some point it had passed through path-

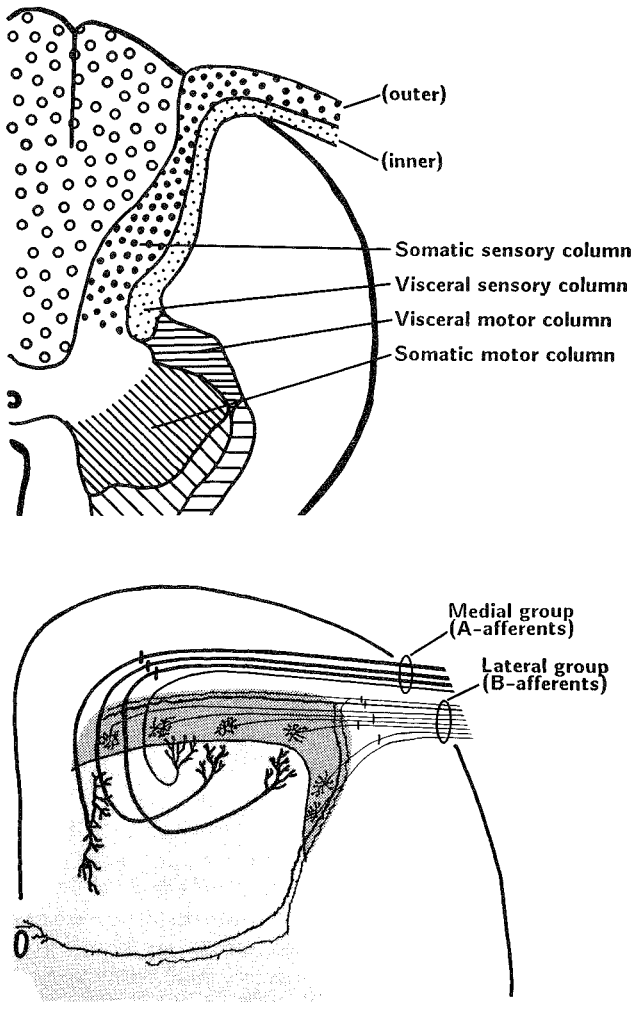


Figure 2. Early and modern views of spinal cord organization. Top (a): Early conception of a cross section of the human spinal cord showing the four columns that were hypothesized to be basic to the doctrine of nerve components. The somatic and visceral sensory columns were considered the projection zones of afferents from outer and inner tissues, respectively. Based on Figure 67 of Herrick's (1927) *An Introduction to Neurology.* Bottom (b): Modern view of spinal afferent organization. In some species, the cutaneous and proprioceptive afferents (the ontogenetically earliest afferents) form a fascicle that enters the spinal cord medially; they have large fibers and collaterals that terminate in the ventral layers of the dorsal horn. (Proprioceptive collaterals are not shown.) The visceral and somatic (cutaneous, articular, muscular), or late-arriving, afferents form the lateral group (lateral group); have small fibers and terminate chiefly in the superficial layers of the dorsal horn (*darkly shaded area*). Adapted from Maxwell & Réthelyi (1987).

ways that Langley had considered a priori to be exclusively "autonomic." Thus, because none of the cutaneous or other nonvisceral afferents took a circuitous path through the sympathetic ganglia, none of them could be considered autonomic. As a result of this approach, the dermis has become a reflexological oddity; its only efferent innervation is autonomic (e.g., vasomotor, pilomotor, sudomotor), and its only afferent innervation is called "somatic." (As will be discussed later, many of these so-called somatic afferents elicit autonomic reflexes when stimulated.)

This dependence on nerve pathway as a classification criterion represents a return to the cerebrospinal system concept of Willis and its functional associations. Langley (1921) objected to using volition as a classification criterion because of its subjectivity, but he persisted with Willis' idea that the cerebrospinal nerves were distinguished by their ability to produce conscious sensations. The observation that sympathetic nerve stimulation produced pain reinforced Langley's view that sympathetic nerve afferents did not differ from other spinal cord afferents and thus should also be considered somatic (Langley 1903, pp. 21, 26).

2.3. Contemporary terms and usages. Currently, different PNS classifications are used for different purposes. Herrick's terminology is used for "visceral" afferents and Langley's term "autonomic" is indispensable for discussing the innervation of tissues that are difficult to describe as visceral (e.g., bone marrow, sweat glands, brown adipose tissue).[1] The term "somatic" is applicable to both systems but its different connotations cause confusion. Some scientists use the term simply to designate those nerves that do not innervate the viscera; others attach functional connotations in the tradition of Langley (e.g., conscious sensation). For example, in one prominent physiology textbook published in the United States (Guyton 1986), visceral pain is listed under the rubric "Somatic Sensations II."

Other classifications of peripheral neurons in addition to the systems of Herrick and Langley have contributed to the current terminology and blend of meanings. Table 1 is a list of these classifications and the criteria used to establish them. The more recent groupings of afferents under the labels "sympathetic" and "parasympathetic" (see Introduction) do not conflict with the B-neuron grouping proposed here; they could include separate subpopulations of B-neurons. The observation that B-neurons are involved in the functioning of autonomic reflexes is a strong argument that they are associated with the ANS. The fact that they are found in sympathetic and parasympathetic pathways is less compelling. Again, as Bell (1811) concluded, nerves do not correspond to specific neuron classes. Many of the accepted nerve labels are either arbitrary or do not accurately indicate their fiber compositions. For example the abdominal vagus, although thought of as a parasympathetic nerve, contains sympathetic (Ahlman et al. 1979) and other yet unidentified fibers (Prechtl & Powley 1987; 1990).

3. A- and B-afferents: Alternatives to somatic and visceral classes

We now know that there are two major populations of afferents in the dorsal root ganglia: the A- and the B-neurons. These two populations are produced by successive waves of cell proliferation (Carr & Simpson 1978, *chick;* Hamburger & Levi-Montalcini 1949, *chick;* Lawson & Biscoe 1979, *mouse;* Lawson et al. 1984, *rat*). The A-neuron class is known to consist predominantly of proprioceptive and mechanoreceptive afferents; the B-class consists mostly of thermoreceptive and nociceptive afferents. Thus far, a nervous system classification has not been proposed that is based on these two afferent populations; rather, the A- and B- designators have been applied

Table 1. *Peripheral sensory neuron classifications*

Work	Classification	Criteria
Head et al. (1905)	Deep sensibility; protopathic sensibility; epicritic sensibility	Function, morphology, receptive field size, regeneration profile
Sherrington (1906)	Proprioceptive; interoceptive; exteroceptive	Function, responses to adequate stimuli
Gasser and Erlanger (1929); Heinbecker et al. (1934)	A-, B-, and C-fibers[a]	Conduction velocity, electrophysiological traits, fiber size
Lloyd (1943)	Afferent groups I, II, III, IV[b]	Reflex type, fiber size, peripheral termination
Contemporary authors	Sympathetic, parasympathetic afferents	Ability to elicit ANS reflexes, found in sympathetic or parasympathetic nerves

[a]Fiber classification includes efferents.
[b]Lloyd's classification was originally formulated for analyzing hind limb reflexes in the cat.

secondarily to the traditional designators, "somatic" and "visceral," and have usually been used only for describing ganglion cell morphology. In this target article we argue that the ontogeny of afferent populations is far more significant and more fundamental than other classification criteria. As will be shown, the A-B distinction seems to be correlated not only with many other distinguishing cell traits and organizational features, but also with a particular class of functions. Put another way, we conjecture that Langley, if he had had access to today's data, would have assigned B-neurons to the autonomic afferent category that he left empty.

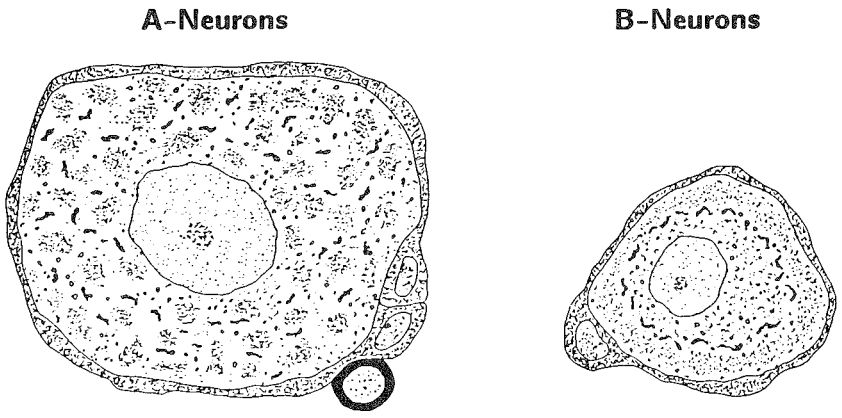
3.1. "Large light" and "small dark" cells. In light-microscopic studies conducted since the nineteenth century, the A- and B-neuron populations have been referred to as "large light" and "small dark" cells (for reviews see Andres 1961; Lieberman 1976; Scharf 1958). The designators "A" and "B" have been applied only recently by electron microscopists. Although some investigators had initially argued that the difference in light-microscopic density of the A- and B-neurons was artifactual, ultrastructural studies have since indicated that it is related to the distribution of Nissl substance and neurofilaments. The A-neurons appear lighter because their Nissl substance is gathered in clumps within a lattice of relatively translucent neurofilament bundles, whereas the somata of the small dark neurons interfere more thoroughly with light because their granular endoplasmic reticulum and free ribosomes are more concentrated and more evenly distributed (see Figure 3). Other ultrastructural features distinctive of the small dark cells (B-neurons) include more highly developed Golgi apparatus, lysosomal bodies, and Golgi-associated smooth endoplasmic reticulum with associated lysosomes (Lieberman 1976), and a concentric zonal distribution of membrane-bound organelles (Rambourg et al. 1983, *rat;* Sommer et al. 1985, *mouse*). With the use of prolonged nerve stimulation and electron microscopy, Duce and Keen (1977, *rat*) demonstrated that the differences in ultrastructure of A- and B-neurons could not be explained on the basis of different activity states.

Although the B-neurons are small, the size distributions of A- and B-neuron populations overlap considerably (Lawson 1979, *mouse;* Lawson et al. 1984, *rat;* J. Price 1985, *rat*). B-neuron cell diameters range from 15 μm to 35 μm; those of A-neurons range from μm 15 to 70 μm, but most are greater than 40 μm. Using computerized statistical analysis, Lawson (1979, *mouse*) demonstrated that the distribution of cell sizes in the DRG can be described by no fewer than two Gaussian distributions.

Other morphological differences are also found at the light-microscopic level. The A-neurons have prominent spiraling glomeruli and have mostly large myelinated fibers. Their unipolar cell stems are also myelinated, and in the central zone of the ganglion, at a node of Ranvier, each stem divides into central and peripheral myelinated processes of roughly equal diameter (Ha 1970, *cat*). The B-neurons do not have complicated glomeruli and most of their fibers are unmyelinated, although some are thinly myelinated (Andres 1961, *rat*). The unipolar cell stem of the unmyelinated B-neurons, and possibly that of the thinly myelinated ones, forms a central process that is several times thinner than either the stem or the peripheral process (Ha 1970, *cat*).

Recently, the presumed A- and B-neuron populations of the rat have been discriminated histochemically. The light-microscopically identifiable A-neurons were found to bind the neurofilament protein antibody RT97 (Kai-Kai et al. 1986, *rat;* Lawson et al. 1984, *rat;* J. Price 1985, *rat;* Sharp et al. 1982, *rat*), and the size distribution of RT97-labeled neurons correlated well with the theoretical statistical distributions generated to describe the cell size distribution of the A-neuron population (Lawson et al. 1984, *rat*). The B-neurons were found to contain arginine vasopressin (Kai-Kai et al. 1986, *rat*). When RT97 and arginine vasopressin probes were applied to adjacent sections of the same DRG, they stained complementary populations.

Although arginine vasopressin may be a marker of all B-neurons in the rat, it has long been known that both overlapping and nonoverlapping subpopulations of B-neurons can be identified by various histochemical markers,[2] which include bombesin/gastrin-releasing peptide (Panula et al. 1983, *rat*), the corticotropin-releasing factor (Skofitsch et al. 1985, *rat*), fluoride-resistant acid phosphatase (Knyihár-Csillik & Csillik 1981, *rat;* J. Price



ONTOGENY	EARLY		LATE
Histochemical Marker	RT97 positive		arginine vasopressin, myelin-associated glycoprotein
Fiber Types	A-alpha & A-beta heavy myelin	A-delta thin myelin	C unmyelinated
Lloyd's Afferent Groups	I II	III	IV
Receptor Endings	encapsulated receptors		bare nerve endings
Modalities	proprioception, discriminative touch		thermoception, nociception, tickle, itch, crude touch

Figure 3. A- and B-neuron characteristics. The essential criterion for grouping B-neurons is a common ontogenetic history. Thus far, B-neurons are known to have been born late and to have a characteristic sensitivity to nerve growth factor during development. Most of the proposed divisions are tentative extrapolations that have not yet been directly tested using the ontogenetic criteria. Although most neurons with fibers that conduct impulses in the A-delta velocity range (*central panel*) belong to the B class, D hair receptor afferents (which also conduct in the A-delta range) may be an exception; their central morphology (see Brown 1981) and electrophysiological properties (see Koerber et al. 1988) differ from those of other B-neurons (A-delta and C-fibers). Neuron illustrations adapted from Rambourg et al. (1983).

1985, *rat*), oxytocin (Kai-Kai et al. 1986, *rat*), somatostatin, substance P (Hökfelt et al. 1976, *rat;* Tuchscherer & Seybold 1985, *rat*), and vasoactive intestinal polypeptide (Lundberg et al. 1978, *guinea pig*). At least one sensory neuropeptide, the calcitonin gene-related peptide, does not seem to be a discriminator of B-neurons because it is found in DRG neurons of all sizes (Ju et al. 1987, *rat*).

The histochemistry and fiber type data suggest that the A- and B-neuron populations are the basis of the principally dichotomous organization of DRG afferents within the dorsal horn that has been summarized or implied in recent reviews (Brown 1981; Cervero 1986; Hunt 1983; Maxwell & Réthelyi 1987; Perl 1984; D. D. Price 1986; Ruda et al. 1986; Willis 1985): Peripheral to or within the dorsal root entry zone, DRG afferent processes are segregated into medial and lateral groups (Figure 2b). The lateral group distinctively contains small, unmyelinated, and thinly myelinated fibers; the medial group contains mostly large, thickly myelinated fibers. Whereas the fibers of the lateral group terminate predominantly in the superficial layers of the dorsal horn (Rexed's laminae I, II, and V), the collateral terminals of the medial group terminate most densely in the more ventral layers (especially laminae III and IV). The termination pattern of the lateral group matches closely the combined termination patterns of the various histochemically identified B-neuron processes (see de Groat 1986; Hunt 1983; Kai-Kai et al. 1986; Ruda et al. 1986). Also indicative of the lateral group's origin is the observation that, like B-neurons, the lateral group appears late in ontogeny, as do the neurons of the superficial layers of the dorsal horn (Altman & Bayer 1984). Moreover, some anatomical features of the two groups may be explained by their different ontogenies. For example, the hair receptor afferents of the medial group characteristically descend medially in the dorsal horn, curve laterally and ascend dorsolaterally, and terminate predominantly in laminae III and IV (see Figure 2b). The developmental explanation for such circuitous paths is that although these early-arriving axons initially form a straight path to rely neurons, they are later dragged ventromedially as the dorsal portion of the developing spinal cord rotates (Altman & Bayer 1984). The

lateral group (B-neuron) processes arrive after the rotation phase and thus do not become distorted.

3.2. B-neurons of different species and developmental stages. Comparative analyses of DRG cytology are not available, but the light-microscopic literature includes reports of similar cell populations in a variety of vertebrates, including the cat, cow, fox, horse, human, lamprey, lemur, mouse, pig, rabbit, and rat (see Scharf 1958). They have also been identified in electron microscopic studies of the rabbit (Dawson et al. 1955; Tennyson 1965), guinea pig (Hess 1955), rat (Andres 1961), frog (Berthold 1966), and mouse (Sommer et al. 1985).

Most studies have reported on the cell structure of the adult ganglia; however, large- and small-celled populations have also been reported in the embryonic ganglia of the chicken (Hamburger & Levi-Montalcini 1949), sheep, rabbit (Tennyson 1965), and mouse (Lawson 1979; Lawson & Biscoe 1979). Furthermore, there is evidence that the large- and small-celled embyronic populations represent immature versions of the A- and B-neuron phenotypes found in the adult. With the use of thymidine labeling, Lawson and Biscoe (1979; also Lawson 1979) demonstrated that large and early-differentiating neuroblasts of the murine DRG mature into A-neurons and that the smaller, late-differentiating neuroblasts mature into B-neurons. A striking feature of the chick embryo DRG is that for a period of development during and after ganglion cell differentiation the two cell types are clearly segregated in different zones of the ganglion (Hamburger & Levi-Montalcini 1949). The large neurons occupy the lateroventral zone (and are thus called LV cells); the small ones occupy the mediodorsal zone (and are called MD cells).

For decades, the two neuron populations of the chick embryo DRG were designated LV and MD cells, and the issue of homology with other adult vertebrate DRG cells did not arise. Recently, however, (Barakat et al. 1985; Philippe et al. 1986) have applied the A- and B-neuron terminology to the chick embryo cells, presumably because myelin-associated glycoprotein immunoreactivity was localized specifically in chick embryo MD cells (Omlin et al. 1984), and this immunocytochemical staining in hatching-age chick ganglion cells was correlated with B-neuron morphology (Philippe et al. 1986). Other grounds for postulating an equivalence between B-neurons and MD cells are: (1) Both MD neurons (Hamburger & Levi-Montalcini 1949) and B-neurons (Lawson 1979, *mouse;* Lawson & Biscoe 1979, *mouse*) are born in the second of the two overlapping waves of cell proliferation. (2) Root ganglion substance P immunoreactivity, which is restricted to B-neurons in the chick embryo DRG, is found only in the MD population (Fontaine-Perus et al. 1985; New & Mudge 1986). (3) These substance P-containing MD neurons project primarily to the avian dorsal horn homologues of Rexed's laminae I and II (La Valley & Ho 1983; New & Mudge 1986), the same laminae to which B-neurons project. (4) The peripheral processes of MD neurons seem to show the same broad distribution as B-neurons (Honig 1982).

3.3. B-neuron metameres in the cranial root ganglia. B-neurons are not restricted to spinal root ganglia but are found also in the metameric (segmentally homologous) ganglia of the cranial nerve roots.

Like the spinal nerves, some cranial nerves (5th, 7th, 9th, and 10th) have dorsally positioned roots and have been called dorsal root nerves (Romer 1970). Most such nerves have two ganglia; the more proximal of the two is known as the root ganglion and is considered a metamere of the spinal root ganglia. The cranial root ganglia, like their spinal counterparts, are embryonic derivatives of the neural crest and include the jugular ganglion of the 10th nerve, the superior ganglion of the 9th nerve, and the cells that occupy the most proximal portion of the trigeminal ganglion in early development. In contrast, the more distal ganglia, such as the nodose and petrosal, have a placodal embryonic origin (Narayanan & Narayanan 1980, *chicken*). The trigeminal nerve ganglion also has placode-derived neurons that aggregate distally in the nerve root (Hamburger 1961, *chicken*), but they do not form an anatomically distinct distal ganglion.

Cranial B-neurons accordingly, have many of the same characteristics as spinal B-neurons, such as late maturation, small cell size, and the presence of substance P (Fontaine-Perus et al. 1985, *chicken*). The presumed trigeminal B-neurons of adult specimens have comparable ultrastructures (Jacobs et al. 1975, *rat;* Peach 1972, *rat*) and have the same neuropeptides: arginine vasopressin, oxytocin (Kai-Kai et al. 1985, *rat*), substance P, somatostatin, and vasoactive intestinal polypeptide (Kummer & Heym 1986, *guinea pig;* see also Ruda et al. 1986). They also show similarly heavy staining for acid phosphatases and acetylcholine esterases, although differences have been found in monoamine oxidase staining (Kalina & Wolman 1970, *rat*). Finally, the afferents of cranial nerves 5, 7, 9, and 10, which would be presumed to be B-neurons because of their fiber type or function (thermoceptive or nociceptive), or the presence of substance P, terminate densely in the spinal trigeminal subnucleus caudalis (Cuello et al. 1978, *rat* [trigeminal substance P]), the medullary continuation of the dorsal horn.

3.4. Lumping and splitting. Thus far, few subpopulations of the A and B classes have been studied in detail, and the existence of additional small but distinct populations cannot be ruled out. Electron microscopists who have systematized the classification of ganglion cells have typically included a transitional group that has the ultrastructural features of both A and B classes, such as the A_3 cell groups of Rambourg et al. (1983, *rat*) and Andres (1961, 7% of *rat* DRG cells). Also, some very small neurons have been distinguished from the B-neurons and are considered to constitute a C class (Rambourg et al. 1983, *rat;* Sommer et al. 1985, 1% of *mouse* DRG cells). These additional groups may account for the 5% of DRG neurons that Lawson et al. (1984, *rat*) were unable to classify with the use of densitometry, or for the RT97 antibody. Although the histochemical markers tested thus far with rat tissue suggest a sharp division among most ganglion cells, future histochemical identifications will have to be correlated with ontogenetic and ultrastructural traits, both within and between species.

As shown in Figure 3, B-neurons have a number of traits that distinguish them from other DRG neurons. Traits such as presence of substance P are not listed

because, unlike the presence of arginine vasopressin, they distinguish only a subpopulation of B-neurons. The demarcation of A- and B-neuron groups proposed in Figure 3 is based primarily on the hypothesis and implicitly accepted principle that ontogenetic history provides the most crucial data for cell classification. Just as phylogenetic history (when it can be deduced) is predictive of the characters and behaviors of related organisms, ontogeny should best predict cell phenotype because it is through modifications of the ontogenetic sequence that cellular specializations emerge. Cell lineage, in combination with epigenetic factors (e.g., timing, position, microenvironment) ultimately determines the differentiated state of the cell; in most instances neurons do *not* become similar as a result of responding to dissimilar ontogenetic variables. Nevertheless, we know little about the rules of ontogeny, or about how to interpret and weight different ontogenetic data. In this target article, the late birth of the B-neuron population is regarded as an indicator of specific developmental potentials that are not possessed by the A-neurons.

The test of this ontogenetically based classification will be whether it can parsimoniously describe the functional organization of the PNS. That is, the information that a DRG afferent belongs to the ontogenetically defined A or B class should tell us more about its structure, connective relations, and function than the information that its peripheral fiber passed through a somatic or visceral nerve.

4. Close relationship of B-afferents and autonomic neurons

An association between B-neurons and the ANS is suggested by the peripheral distribution of B-afferents, by their role in homeostatic reflex functions (section 5), and by the fact that virtually all root ganglion visceral afferents belong to this population. Often cell populations with collaborative or closely related functions have similar phenotypic and ontogenetic traits (e.g., T- and B-lymphocytes), and this seems to be true of B-neurons and ANS neurons.

4.1. Phenotypic similarities. At the most superficial level, B-neurons, with their less differentiated morphologies, tend to resemble principal (postganglionic) autonomic neurons. The small dark cell types in some preparations have been mistaken for genuine sympathetic neurons. For instance, having used a prolonged osmium stain, Kiss (1932) maintained that the large groups of DRG cells (B-neurons) found in numerous vertebrates were actually ectopic sympathetic neurons. Moreover, in mammals, most sympathetic and B-neuron fibers are histologically indistinguishable (Gasser 1955) and conduct impulses in nearly identical velocity ranges – from 0.7 to 2.3 m/sec for superior cervical ganglion sympathetics; from 0.6 to 2.0 m/sec for dorsal root C-fibers (Patton 1960, p. 77). In contrast, most somatic (skeletomotor) efferents and afferent A-neurons conduct impulses at velocities several times greater.

A number of histochemical similarities have also been found between sympathetic[3] neurons and certain subpopulations[4] of B-neurons. For example, like many B-neurons, sympathetic neurons contain substance P (Kessler et al. 1981, *rat*). Substance P has also been found in a variety of preganglionic ANS neurons, including sympathetic preganglionic neurons (Krukoff 1987, *cat*), preganglionic neurons extending to the ciliary ganglion (Erichsen et al. 1982, *pigeon*), and vagal preganglionic neurons extending to the cardiac ganglion (Bowers et al. 1986, *bullfrog;* Gibbons et al. 1987, *toad*). Other histochemical markers found both in the sympathetic ganglia and in subpopulations of B-neurons are tyrosine hydroxylase (J. Price 1985, *rat*), somatostatin, and vasoactive intestinal polypeptide (Fontaine-Perus et al. 1985, *chick embryo;* Lundberg et al. 1982, *guinea pig*). Finally, myelin-associated glycoprotein immunoreactivity, which is a marker of B-neurons in the chick embryo (see section 3.2), has also been found in cells of the sympathetic ganglia and adrenal medulla of the same preparation (Omlin et al. 1984).

4.2. Ontogenetic parallels. Perhaps the most significant ties between sympathetic and B-neurons are their late ontogeny and exceptional sensitivity to nerve growth factor. In a now historic experiment, Levi-Montalcini and Hamburger (1951) observed the morphological effects on a chick embryo of a factor released by grafted mouse sarcoma tumor fragments. The tumor fragments were grafted unilaterally to the base of a limb bud in 1.5- to 3-day-old chick embryos. When embryos were histologically examined on embryonic days 5 and 6, the untreated limb showed the normal combined ingrowth of the LV neurons (embryonic A-afferents; see section 3) and skeletomotor efferents; in the tumor-bearing limb the LV fibers either bypassed the tumor or were blocked by it. In contrast, the embryos that were examined at later dates – once the MD cells (chick embryo B-neurons) and sympathetic neurons had differentiated and extended neurites – exhibited a striking effect: the sympathetic ganglia and MD (B-neuron) zones of the dorsal root ganglia were hyperplastic, and these two neuronal groups had caused a "hyperinnervation" of the tumor. In the fifties, the substance responsible for these trophic and morphogenetic responses was isolated and named nerve growth factor (NGF; for review see Levi-Montalcini 1987).

More recently, NGF has been found to have a variety of trophic effects on a number of cell populations; sympathetic neurons (except "short-type" sympathetics; see Harper & Thoenen 1981) and B-neurons, however, provide the broadest demonstration of NGF's activities, including neurite extension and guidance (Levi-Montalcini 1987). These late-developing efferents and afferents may depend partly on NGF as a chemotactic or haptotactic factor for approximating their target tissues, even though much of their anatomical course has already been paved by the earlier-differentiating skeletomotor and A-neurons. Such a morphogenetic action could help explain the comparably broad innervation patterns of sympathetic and B-neurons and the observation that they jointly innervate some tissues to the exclusion of all other neuron types (e.g., cornea, Tervo et al. 1979; bone marrow, Bulloch 1985; sweat glands, Hökfelt et al. 1975). By citing as an example the responsiveness of these neuron groups to NGF, Black (1986) has suggested that conjoint responsiveness to trophic factors represents an evolutionary mechanism for regulating coinnervation

(e.g., adjustment of relative pathway size). Whether NGF played a role in evolution or even affects normal morphogenesis is still unclear; it is of interest here, however, that sympathetic and B-neurons show the same exceptional responsiveness to NGF both in vitro and in vivo.

Levi-Montalcini & Hamburger's (1951) study of the chick embryo serves to contrast the developmental timing of A- and skeletomotor neurons with that of B- and sympathetic neurons. This differential timing is also reflected in the ontogeny of reflex functions in mammals. Proprioceptive and exteroceptive reflexes appear early, in utero (see Windle 1944), whereas sympathetic (Smith et al. 1982, *rat*) and other C-fiber reflexes (Fitzgerald & Gibson 1984, *rat*) do not mature until well after birth. Although postnatal B-neurons no longer respond to NGF with neurite extension, most B-neurons, like sympathetic neurons, continue to show biochemical responses to NGF. Sympathetic neurons respond to NGF by increasing their levels of catecholamines (Harper & Thoenen 1981); the somatostatin- and substance P-containing B-neurons respond by increasing their respective neuropeptide contents (Kessler & Black 1981, *rat*).

A final ontogenetic argument for the relatedness of B-neuron and sympathetic cell types comes from results suggesting that they have similar developmental potentials. Until embryonic day 10, the cells of quail dorsal root ganglia back-transplanted into young (day-2) chick embryos migrate to the sympathetic ganglia and adrenal glands and differentiate into adrenergic phenotypes (i.e., sympathetic and chromaffin cells; for review, see Le Douarin 1982). Also, under specific conditions, cultured DRG cells are able to differentiate into catecholaminergic (sympathetic) neurons (Newgreen & Jones 1975, *chicken;* Xue et al. 1985, *quail*). The undifferentiated DRG cells that are capable of becoming sympathetic neurons may perhaps represent the same (or similar) precursors that have been found to differentiate under other culture conditions into small neurons that are immunoreactive for substance P and for myelin-associated glycoprotein (i.e., B-neurons; Barakat & Droz 1987).

5. Functional ties between B-neurons and autonomic neurons

The similarity between sympathetic and B-neuron phenotypes is also reflected in their functional relations. By extrapolation from both fiber size and the conclusion that B-neurons are the afferents of layers I & II of the dorsal horn, we can infer that the "modalities"[5] mediated by B-neurons include thermoception, nociception, tickle, itch, and crude (C-fiber) mechanoreception. Some B-afferents, therefore, must constitute the afferent limb of thermoregulatory and nociceptive sympathetic reflexes (see Jänig 1985). Moreover, it is becoming increasingly clear that sympathetic and peptidergic B-neurons jointly mediate the neural control of the immune system (Felten et al. 1985; Payan et al. 1986).

Although thermoregulation and immunomodulation are generally considered autonomic functions, nociceptive reflexes associated with pain perception are often regarded functionally as "somatic" (see section 2.3). However, recent evidence from substance P-containing B-neurons (SP-B neurons), the most thoroughly characterized nociceptive afferents, affirms that nociceptive reflexes invariably and most directly involve the ANS or autonomic effectors.

5.1. SP-B neurons and rejective reflexes. Substance P-containing afferents represent a major subpopulation of B-neurons, by far the most studied ones. In rats SP-B neurons amount to from 10% to 30% of DRG neurons (Hökfelt et al. 1976; Kai-Kai et al. 1986), or as much as half of all B-neurons, depending on the segmental level sampled. The peripheral terminals of SP-B neurons are highly collateralized and broadly distributed via visceral and somatic nerves to a variety of tissues, including autonomic effectors. Some SP-B neurons have collaterals that also terminate in autonomic ganglia (Hökfelt et al. 1977; *cat, guinea pig, rat;* see Figure 4).

For the most part, SP-B neurons mediate reflexes that are elicited by injurious or potentially injurious stimuli (noxae), some of which contribute to pain perception (Henry 1980). In 1937, these and other B-afferents that mediate protective reflexes in the skin were described as constituting a "nocifensor" system by T. Lewis (see Lembeck 1985; 1987). It now seems clear that the afferents that mediate analogous reflexes in the eyes and mucous membranes and have been known as the "common chemical sense" (see Moncrieff 1967) belong to the same system.

SP-B neurons mediate protective reflexes in three different ways. First, they mediate them in the least direct way by releasing substance P (and perhaps other neuroactive substances) to interneurons and to the interstitial space of the spinal cord. Physiological studies have shown that intrathecal substance P facilitates the flexor withdrawal reflex in response to noxae (Wiesenfeld-Hallin 1986, *rat*). Second, they mediate such reflexes more directly (monosynaptically), by releasing substance P antidromically from axon collaterals that terminate on principal autonomic ganglion neurons. SP-B neurons have been found to form axodendritic synapses with prevertebral sympathetic neurons (Matthews et al. 1987, *guinea pig*); when stimulated, they produce slow, excitatory, postsynaptic potentials (Otsuka & Konishi 1983, *rat*). Finally, SP-B neurons mediate protective reflexes most directly by releasing locally in the effector tissue transmitter from stimulated nerve terminals or from the antidromically excited terminals of neighboring collaterals. These local terminal and axonal reflexes provide the least ambiguous definition of SP-B neuron function because they are fixed and independent of synaptic or integrative factors.

Local SP-B neuron reflexes vary from tissue to tissue, but in general they are rejective or immunologic (see Table 2) – that is, they purge, neutralize, or bar potentially harmful elements from epithelia or interstitial spaces. Since the writings of Bernard (1878, 1973), the interstitial fluid of tissues has come to be regarded as a carefully regulated milieu of electrolytes, gases, nutrients, thermal energy, and metabolic by-products. The external environment is recognized as the source of nurture, but also as a threat. Homeostasis consists of the carefully monitored exchange between the two environments, the assimilation of nutrients and warmth, and the rejection of noxae and foreign elements. Rejective reflex-

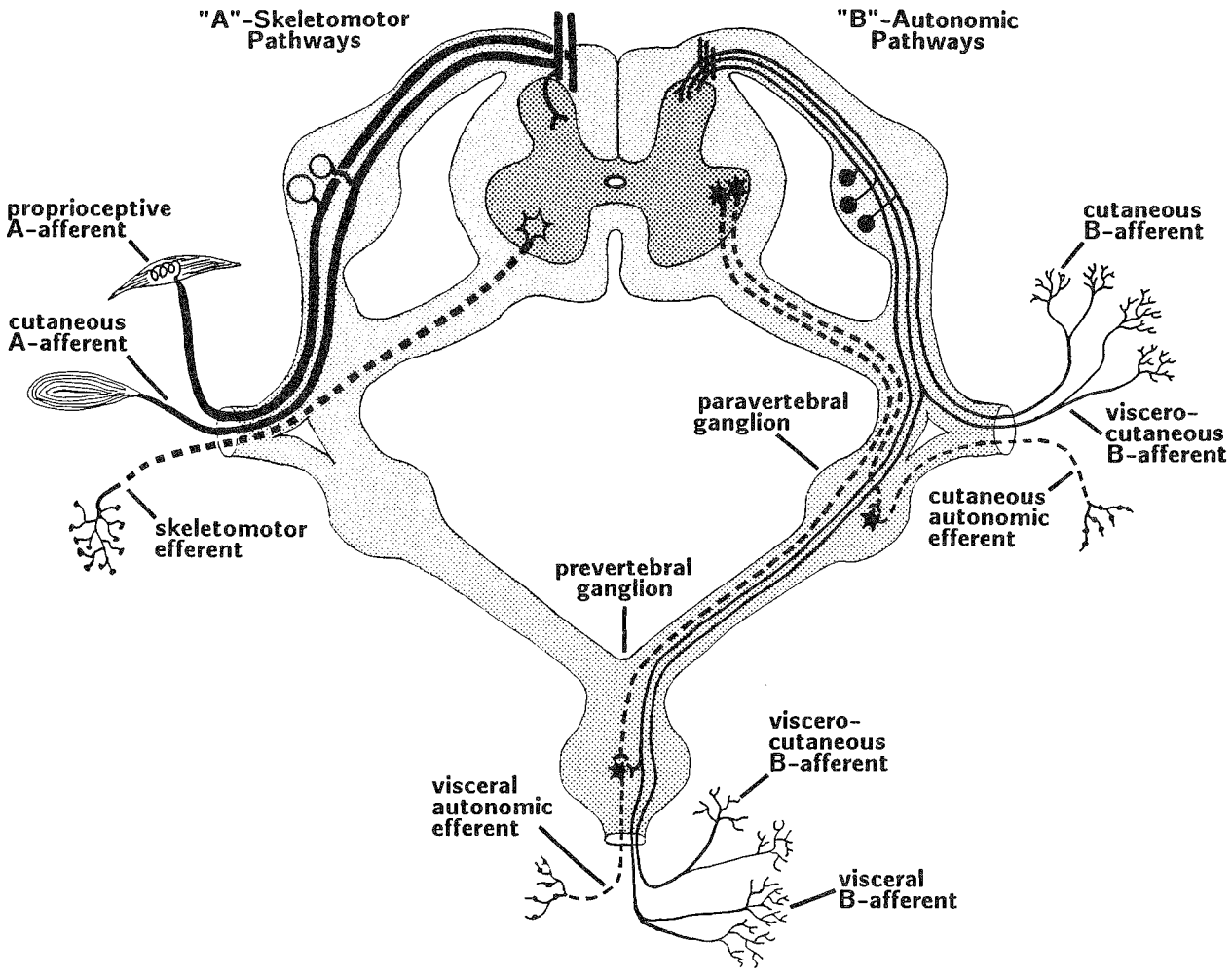


Figure 4. Afferent and efferent components of the spinal nerves and ganglia. The left-hand side shows the A-afferent and skeletomotor (somatic) efferent (*dashed line*) divisions. The right-hand side shows the B-afferent and autonomic efferent (*dashed lines*) divisions. The viscero-cutaneous (or possibly viscero-muscular) neuron has collaterals that dichotomize into visceral and somatic pathways. (Drawing based on the electrophysiological data of Bahr et al. 1981). The collateral innervation of prevertebral ganglia is consistent with findings that have been reported on substance P-containing B-neurons. Adapted in part from Carpenter (1976, p. 232).

es are therefore particularly important in tissues that are at risk, such as those which are specially adapted for nutrient assimilation, blood-gas exchange, thermal exchange, waste concentration, and certain sensory functions (e.g., nasal mucosa).

Although many SP-B neuron reflexes could be described as rejective because they function to minimize the immediate effects of eliciting stimuli, it is doubtful that a single term can describe all of their actions. Furthermore, the visceral and somatic varieties of SP-B neurons are not likely to be functionally identical, because their projection patterns within the superficial dorsal horn have been found to differ slightly (Cervero & Connell 1984, *cat*). Nevertheless, comparisons using a number of criteria, including the role in the defense of homeostasis, indicate that inner and outer SP-B neurons are far more alike than their "visceral" and "somatic" labels would suggest.

The role in the defense of homeostasis is not restricted to B-neurons that contain substance P. Recently, Lembeck (1987) summarized a number of findings on capsaicin-sensitive B-afferents (SP-B neurons included) and hypothesized that such afferents constitute a "neurogenic alarm system" or a "network of defense." The defensive reflexes he cites include neurogenic inflammation, heat loss thermoregulation, micturition, sneezing, lacrimation, salivation, splanchnic depressor responses, protective skeletomotor reactions, and a number of endocrine responses such as catecholamine release in response to hypoglycemia (see also Lembeck 1985). In general, Lembeck's (1987) insightful interpretation of capsaicin-sensitive B-afferents is compatible with the hypothesis of this target article. In support of the argument developed here about ANS relations, however, we would emphasize that the role of B-neurons in skeletomotor and behavioral defensive reflexes is functionally and synaptically less direct than in autonomic reflexes. Only autonomic neurons and autonomic effector tissues have been shown to be directly excited by B-neurons.

The boundaries outlined in Figure 3 suggest that B-neurons also include mechanoreceptive C-fiber afferents that are neither nociceptive nor capsaicin-sensitive (Fitzgerald 1983). If by ontogenetic definition these afferents are truly B-neurons, then a test of the present

Table 2. *Local rejective reflexes of SP-B neurons*

Tissue stimulus	Response	Function
Injury to/irritation of skin and various mucosae	Histamine release;[a] plasma extravasation[a]; stimulates or increases T- and B-lymphocytes[b]; enhances phagocytosis[b]	Immunologic: restricts spread of foreign or noxious elements; resolves infection
Eye injury	Miosis[c]; aqueous flare[c]	Minimizes stimulation; immunologic
Nasal irritation	Stimulates or increases mucociliary action,[d] secretions[e]	Purges nasal mucosa; immunologic
Airway irritation	Stimulates or increases tracheal secretions[b]; broncoconstriction[f]; plasma extravasation[f]	Purges epithelium; minimizes exchange of airborne contaminants; immunologic
Intestinal irritation	Hypersensitivity reaction (spasm)[g]	Minimizes absorption of irritants?
Bladder infection	Reflexive micturition[h]	Ejects chemical irritants

Note: The most recent reference or best source of references is cited.
[a]Lembeck 1985.
[b]Payan et al. 1986.
[c]Håkanson et al. 1985.
[d]Lindberg & Mercke 1985.
[e]Lundblad et al. 1983.
[f]Lundberg et al. 1985.
[g]Goetzl et al. 1985.
[h]Maggi & Meli 1986.

hypothesis would be to examine whether their synaptic and functional relations are most direct with the ANS, or with skeletomotor neurons. Similarly the present hypothesis would predict that in the cat most visceral afferents have more in common with somatic B-afferents than with the exceptional *A-beta* visceral afferents (see section 2.2) because the A-beta visceral afferents, as judged by their fiber types, are probably not B-neurons, whereas most visceral afferents are.

6. Implications

One implication of our second hypothesis is that nociceptive reflexes are simply one of a variety of autonomic reflex types. The autonomic correlates of nociception have traditionally been thought of as epiphenomena, that is, nonessential symptoms or indexes of nociception, and as examples of "somatic-autonomic" integration. According to the present model, nociception and ANS function are simply the afferent and efferent aspects of the same reflex arc. The validity of this perspective is borne out by the observation that PNS disorders that involve nociceptive B-afferents – such as cluster headache (Hardebo 1984), familial dysautonomia (see Pearson et al. 1982), and reflex dystrophies (see Procacci & Maresca 1987) – invariably involve abnormalities in autonomic function. Dyck et al. (1983) have coined the term "hereditary sensory autonomic neuropathy" to refer to a number of disorders characterized by insensitivity to noxious stimuli and autonomic symptoms, and by the involvement of both small afferent and autonomic fibers. Also, because of the traditional PNS classification systems, clinical terminology has varied and has often encouraged different pathophysiological hypotheses (Procacci & Maresca 1987). For instance, some schools of neurology refer to causalgia and similar disorders as *algo*dystrophies, whereas others call them *sympathetic* dystrophies. The difference in terminology and concept can be traced to Langley's "autonomic nervous system" concept and its continual rejection by some of the European schools (see Procacci & Maresca 1987).

The most fundamental issue raised by the present hypothesis concerns the meaning of cell phenotypes with respect to the evolution of the nervous system. Some boundaries between the A- and B-neuron populations depicted in Figure 3 may be inaccurate, but if the proposition is generally correct, a question about the significance of this cytological discontinuity arises. Why is it that thermoreceptive and nociceptive afferents are born late, and discriminative mechanoreceptive and proprioceptive afferents are born early?

One possibility is that the discontinuity reflects an evolutionary shift from homeostatic nervous function alone to a function that includes behavior or skeletomotor maneuvers. According to Romer (1970), the ancestor of the vertebrates was a passive, sea-dwelling filter-feeder with a life-style much like that of an intestine. Somatic function evolved with the addition of locomotor devices such as tails and fins. Romer hypothesized that the original visceral and somatic components were so distinct anatomically and functionally that they could be thought of as two different animals that had been welded together. Although the two components have become progressively more integrated, in Romer's words (1970, p. 29), the "weld" is still an imperfect one.

Many scientists would judge the A-afferents to be more phylogenetically derived in terms of fiber type (Bishop 1959) and receptor ending specializations (Piéron 1952); moreover, these neurons give rise to the lemniscal system (see Mountcastle 1961). The evolutionary innovation represented by the appearance of A-afferents could be

the ability to handle highly discriminative and rapidly changing information about spatial relationships between the animal and the external environment. The primitive B-neurons, on the other hand, seem to be well suited for handling the kind of control system information necessary for the simple increases or decreases characteristic of homeostatic adjustments.

In summary, the variation on Romer's (1970) "imperfect weld" interpretation suggested here is simply that the B- and A-neurons represent the descendant afferents of old and new nervous systems, the old one being originally charged with homeostatic functions and the new one charged with the reconnaissance and behavioral operations necessary for active animal-environment relations.

NOTES

1. There appears to be no consensus as to what a viscus is. Kuntz (1953) extended the definition to include glands and blood vessels – presumably grouping together all of the effectors innervated according to Langley's ANS concept. For a lively exchange on this unresolved issue, see Dart (1922) and Herrick (1922).

2. Words that refer to histochemical markings, such as "immunoreactive," "content," and "labeling," should be taken to mean like immunoreactivity.

3. Currently, too little is known about the autonomic ganglia in general to pursue the idea that B-afferents are specifically related to sympathetics – or, for that matter, that sympathetics and parasympathetics constitute valid afferent cell classes. Similarly, the hypotheses developed here are restricted to B-afferents because relatively little is known about other afferents that are also involved in autonomic reflexes, including the so-called special visceral afferents. The same reservations preventing their incorporation into a more global classification scheme with B-afferents pertain to the enteric plexuses, the intrinsic sensory neurons that are thought to constitute the third subdivision of the ANS (see Figure 1). To paraphrase Langley, further progress awaits the discovery of distinguishing histological characters.

4. Many traits are shared only by subsets of either B-neurons or ANS neurons; nevertheless, they may be regarded as evidence of a relationship. Such traits are called polythetic, as are the taxa they indicate (see Mayr 1982, p. 189; Sneath 1962). For membership in a polythetic taxon, no single trait is either necessary or sufficient.

5. In this article the word "modality" is used only in a loose sense in order to help identify the afferents in question; its use does not indicate an endorsement of any rigorous form of specificity theory.

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Classification of afferents by input not by output?

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It is sometimes said in jest that research in anatomy progresses not through the discovery of new structures but through the renaming of old ones. On initial cursory reading of the target article, it appeared to be a good example of the genre; closer inspection, however, revealed that the article not only critically reviews the debate about the naming of the afferent nerves associated with the autonomic nervous system (ANS) but it also exploits this debate as a vehicle for suggesting a novel division of the peripheral nervous system on complementary functional and structural grounds. In introducing the term "autonomic nervous system," Langley (1921) included an explanatory statement: "It is more important that the new word should be used for new ideas than that the words should be accurately descriptive." Prechtl & Powley's (P & P's) review is written in the spirit of this statement and our criticisms essentially revolve around the "idea" rather than the nomenclature.

The presence of afferent axons in nerves that Langley regarded as part of the ANS has been demonstrated by histological and neurophysiological studies and is not a matter of dispute; but their designation as autonomic afferents is contested. On several grounds, P & P propose that the well-described B-afferents are in effect the anatomically distinct group of afferents sought by Langley as the afferent arm of the ANS. It appears to us that at best the B-afferents can be only a component of the autonomic afferent system (if, for the moment, one excludes the B-afferents supplying the skin; see below).

Vagal afferents supplying the cardiovascular, respiratory, and digestive systems probably outnumber afferents traveling with sympathetic nerves such as the splanchnic, and yet the scheme proposed excludes them from being autonomic on the grounds that they do not fulfill the criteria for being B-afferents (e.g., they are of placodal rather than neural crest origin). If we exclude vagal afferents from P & P's classification, where do we put them? They clearly convey information to the central nervous system (CNS), give rise to sensations by pathways (as indirect as, for example, splanchnic afferents), influence autonomic efferents in response to both noxious and innocuous stimuli (Andrews 1986) and, as with the B-afferents, are involved in rejective reflexes. P & P claim that their classification is more parsimonious; we agree, in the literal sense of the word, which means "stingy" (Oxford English Dictionary); and P & P have indeed been stingy in including only a minor population of the afferents associated with the ANS.

The role of a classification is to reduce complexity, but this new one will, we fear, increase it, not least because of its omission of several cranial afferents, particularly the vagus. Langley's classification shaped the concept of the ANS, particularly in the time before unmyelinated fibres could be easily studied. There is now sufficient evidence, however, to question the continuing value of his scheme and to assess whether we should bolster it further by fitting new data into it rather than by replacing it totally.

From an examination of the basis for ascribing an autonomic afferent role to the B-neurones, P & P extend the observations to propose the hypothesis that the B-afferent system (cutaneous and visceral components) is the substrate of a more fundamental division of the nervous system mediating homeostasis. This is a very interesting idea and meshes with a novel view of homeostatic mechanisms published by one of us (Lawes 1989). We believe that a consideration of homeostatic mechanisms allows a true reconciliation of the functional and anatomical classification

of B-afferents and non-B visceral afferents; we therefore propose the following scheme for discussion:

The distinction between A- and B-afferents is not their connection to skeletomotor and autonomic efferents, respectively. Neither does the autonomic regulation of homeostasis necessarily precede the skeletomotor equivalent. The original contribution of the nervous system to homeostasis was predominantly skeletomotor: Afferents detected suboptimal conditions and skeletomotor efferents withdrew the organism to a more conducive environment. Only later in phylogeny did the central nervous system acquire greater control of smooth muscle and glands and allow the autonomic mediation of homeostatic mechanisms so prevalent in mammals.

Thus, skeletomotor escape/avoidance behaviour preceded autonomic regulation, at least as far as thermoregulation and osmoregulation are concerned. Afferents such as thermoreceptors (including cutaneous ones), presumably of the B-group, were therefore originally linked to protective behaviour expressed via skeletomotor efferents. Nociception, a prominent function of B-neurones, fits readily into this scheme. The function of B-afferents is not autonomic per se, but the detection of any threat, whether autonomic and requiring a homeostatic response or somatic and requiring a skeletomotor response. Conversely, A-afferents detect and discriminate stimuli that are in themselves not threatening and do not require escape/avoidance or autonomic arousal. In this scheme, the role of the non-B afferents (e.g., nodose components of the vagus) becomes clearer. They are a further component of the division of the nervous system mediating homeostasis and protection from harmful stimuli; emesis, in particular, illustrates how wrong it is to try to separate skeletomotor and autonomic function as there is a considerable involvement of both (Andrews & Hawthorn 1987). It is the *purpose* of the response and not its mechanism of mediation that is the crucial criterion.

In conclusion, the concept of A- and B-neurones is a good one, but it should be extended to include other afferents that have similar properties, for example, those of the vagal nodose ganglion. Now we can abandon fruitless semantic arguments over whether there are skeletomotor and not autonomic afferents, or some somatic afferents that more closely resemble visceral afferents. Once attention is turned to what the afferents *do* for the animal, these difficulties are resolved, and the biological significance of striking anatomical and biochemical differences is revealed.

To classify or not to classify: That is the question

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I have enjoyed reading Prechtl & Powley's (P & P's) target article as it is not usual to find scientific articles addressing general questions far beyond the minute details of fragmented data. It is good to know there are neuroscientists who can think of the nervous system as something other than a useful collection of ion channels!

I suspect, however, that there are at least two main reasons why such articles as this one are uncommon nowadays. First, very few journals – though *Behavioural and Brain Sciences* is one of them – publish papers that address general issues rather than specific items of data. Second, and in this case more important, we have acquired so much detailed information on the organization of the nervous system that it is virtually impossible to generalize without the exemptions outweighing the rules.

The kind of grand classification of the different elements of the nervous system prominent at the turn of the century and so well reviewed by P & P (Langley, Gaskell, and the rest) was largely because little detailed information existed on those individual elements, such as their anatomical, electrophysiological, and neurochemical properties. Speculation has always been inspired when not too much is known about an issue. My main objection to another grand classification of the peripheral nervous system along the lines of P & P is, therefore, that these generalisations are no longer helpful because we are now forced to twist many experimental observations to make everything fit into a grand scheme. It is true that the current classifications of the peripheral nervous system are a bit of a mess (and P & P bring this point home very well), but does the new proposal of two distinct categories of primary afferent neurone agree with all the available data? Let us consider a few items:

(i) One of the most powerful spinal actions of afferent C-fibres is the activation of somatic motoneurones. In fact, not only can afferent C-fibres excite flexor motoneurones but they can also increase the excitability of the flexion reflex for prolonged periods of time. Yet P & P play down these affects as "less direct" than the activation of autonomic systems.

(ii) The neurotoxin capsaicin affects afferent C- and A-delta fibres but the functional properties of capsaicin-insensitive afferents connected to nociceptors are all similar to those of capsaicin-sensitive ones. Hence, it is not right to imply that capsaicin is a neurotoxin specific to B-afferents.

(iii) It is possible to dissociate (anatomically, functionally, and behaviourally) the somatic components of nociceptive reflexes from the autonomic responses to a noxious stimulus. The central organization of these two reflex actions is quite different even though they may share a few common elements. I do not think that somatic nociceptive reflexes are simply a variety of a general autonomic reaction.

(iv) Although anatomical evidence exists for dichotomizing afferent fibres with branches in somatic and visceral nerves, no one has yet shown that these branches are connected to functionally active sensory receptors (as implied in P & P's Figure 4). It is important to point out that several investigators have tried (and failed) to find such dual receptive sites, as this is essential for a dichotomizing afferent fibre to have any real functional significance.

(v) One of the most powerful inputs to preganglionic sudomotor neurones is mediated by cutaneous Pacinian corpuscles that are connected to the largest and fastest myelinated somatic afferents. This is an example of an autonomic reflex input entirely supported by A-afferents and hence a major exemption to P & P's classification.

So, the problem is not whether or not there are B-afferents but whether or not it is possible to classify primary afferent neurones into only two major categories and expect that all known properties of these neurones will fit neatly into this pair of very distinct bins. I was not persuaded by P & P's arguments; rather, I still think there are many different classes of primary afferent neurone. Under certain functional or behavioural circumstances, some of these distinct primary afferents can appear to have a common function, but I doubt that this major classification of the peripheral nervous system is useful or justifiable.

How does the B-afferent classification apply to vagal afferent neurons?

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In their thought-provoking target article on B-afferents, Prechtl & Powley (P & P) raise a number of interesting hypotheses

regarding the distinguishing characteristics of B-neurons and their role in visceral reflexes and homeostasis. We are in general agreement with their basic concept that A- and B-afferents have many distinguishing cell traits and that these also correlate with major organizational and functional differences: with the B-afferent neurons subserving an autonomic (visceral) afferent function. P & P's review is based largely on an analysis of the properties of spinal afferents; there is little consideration of parasympathetic and, in particular, vagal afferents, which is surprising, given the authors' significant contributions to our knowledge of vagal morphology. In this commentary, we would like to consider the extent to which P & P's concepts apply to the vagal afferent nerves.

The first point to consider is whether the characteristics that distinguish A- and B-afferents in dorsal root ganglia apply also to nodose ganglion cells. There are certainly two populations of neurons based on cell size and staining properties (positive or negative) with the neurofilament marker RT-97 (Lawson et al. 1984). There is also a third population of neurons, however, that stain weakly for RT-97. It is also evident that many nodose ganglion cells do not show peptide immunoreactivity (for example, substance P or CGRP) or acid phosphatase activity (Dodd et al. 1983). In particular, a very low proportion (less than 5%)of identified gastric vagal afferents contain peptides (Dockray 1988); hence, histochemical stains are not good markers of vagal afferent neurons.

As stated by P & P, nodose ganglion cells are of placodal origin, whereas spinal ganglion neurons are derived from the neural crest. Thus, nodose ganglion cells share only some of the features that distinguish A- and B-afferents. It is possible, however, to distinguish two classes of nodose ganglion neurons electrophysiologically (A- and C-neurons, as described by Gallego & Eyzaguirre 1978) and these classes show marked differences in their sensitivity to chemicals such as 5HT, bradykinin, and, particularly, capsaicin. Type-C afferent neurons in the nodose ganglion are considerably more sensitive to these substances than are the A-afferents (Higashi 1986; Marsh 1987). It is interesting to note that, on the basis of capsaicin-sensitivity, it is possible to distinguish two classes of neurons in the spinal ganglia (Szolcsanyi 1984) and in most ways these correspond to A- and B-afferents as described by P & P.

A consideration of the above leads naturally to the second point. It is quite evident that substantial differences exist between visceral afferents in the spinal nerves and those in the vagus. These differences extend beyond simply those characteristics used to distinguish between A- and B-neurons. For example, in section 3, P & P discuss the similarity between B-afferents and autonomic neurons. One of the characteristics they discuss is the response of these neurons to nerve growth factor (NGF). There are substantial differences in the way nodose ganglion cells respond to NGF. Unlike sympathetic and spinal ganglion neurons, NGF is not necessary for the survival of nodose ganglion cells in vivo or in vitro, although it can enhance substance *P* expression in some cells (Maclean et al. 1988). There are similarities, however, between vagal afferent and sympathetic neurons. Vagal afferents have, in general, slowly conducting, unmyelinated axons, and a population of nodose ganglion neurons contains tyrosine hydroxylase immunoreactivity. It is not yet clear to what extent vagal afferents may be involved in "axon" or "rejective" reflexes, but there is evidence for vagally mediated axon reflexes in the stomach (Delbro et al. 1982).

In one of the footnotes to their target article, P & P raise the question of whether there is sufficient knowledge of different autonomic ganglia to justify a further subclassification of visceral afferents into "sympathetic" and "parasympathetic." We believe that even considering the relatively few differences we have highlighted in this short commentary (and a more expansive review would have added many others), there certainly is a basis for regarding spinal and vagal visceral afferents as distinct cell classes. On organizational principles, the vagus is clearly an autonomic nerve; therefore, based on the arguments outlined above, we think the hypothesis that B-afferents are the sole class of autonomic afferents "Langley was looking for" may be somewhat of an oversimplification.

B-afferents: Is an anatomic definition sufficient to characterize the organization of neural function?

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Prechtl & Powley's (P & P's) target article addresses two notions regarding Langley's (1921) assertion that the autonomic nervous system is exclusively an effector system: (1) that the assertion is influential in shaping modern ideas about the functional organization of the peripheral nervous system, and (2) that the assertion has influenced modern concepts about the structural organization of the nervous system. I believe it would be more accurate to characterize Langley's notion about the function of the autonomic nervous system as a dead issue that refuses to stay buried.

Physiologists and behavioral scientists merely ignore Langley's assertion because they recognize it is wrong from a functional perspective for the following reasons: (1) visceral afferents are the only possible mechanisms for the existence of central neural-evoked potentials in response to visceral stimulation; (2) visceral afferents are essential components of cardiovascular control systems such as the baroreflexes or chemoreflexes; (3) visceral sensations are necessary to account for the repeated observation that interoceptive, Pavlovian conditioning occurs – i.e., conditioning in which the unconditioned stimulus (UCS), conditional stimulus (CS), and conditioned response (CR) all are visceral; and (4) there are a host of perceptible visceral stimuli such as bladder fullness or premature ventricular beats – n.b., patients usually report sensing the premature beat, not the compensatory pause (Kline & Bidder 1946).

On the other hand, neuroanatomists do take Langley's formulation very seriously, because they seem to have an unquenchable need to define neural function – which is organized not only in space but also in time – entirely in structural terms. It is fascinating, however, that although they search for structural bases for classifying neural organization, they continue to acknowledge the need to associate a specific structure with a unique set of functions: Even P & P do that (see section 4 of the target article). Thus, for me the question raised by this paper is not whether B-neurons mediate visceral sensations, but why a structural definition needs to be invoked to characterize a functional organization.

I want to be clear. I have no argument with the scientific value of anatomical description and taxonomy. Structural taxonomies provide very important models for studying physiological functions. The physiological functions and their mechanisms, however, often transcend specific structures. To cite just one example, consider the traditional anatomical classification of nerves as afferent or efferent: Now tell me whether a post-synaptic inhibitory potential is an efferent response or an afferent stimulus? Does this example mean that the afferent/efferent model is not useful? Of course not. It merely means that one conceptual system (afferent vs. efferent) overlaps but is not identical with another conceptual system (stimulus vs. response). As long as one understands the conceptual level at which one is operating, all is well. As soon as one attempts to "explain" the conceptual system of another by subtly redefining the other

person's concept, however, one is going to transform a non sequitur into a controversy. Everyone involved in the [psuedo] issue will end up wasting a great deal of time insisting the other fellow is wrong when, in fact, the problem is that everyone is talking and no one is listening.

Incidentally, I do not believe that neuroanatomists are alone in their effort to redefine function purely in terms of structure. Molecular geneticists are avidly characterizing a host of protein precursor genes and then naively ascribing functions to them.

I hope that the B-neurons turn out to have consistent properties that enable neuroanatomists to classify them into a coherent conduction system. But Langley's assertion is functional nonsense, a cul-de-sac on the path to understanding.

Let afferents be afferents

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Prechtl & Powley (P & P) have presented a convincing case for the existence of a class of primary afferent neurons that exert an influence on autonomic function and "homeostasis." They propose that the B-neurons may subserve autonomic afferent functions on the basis of anatomical, histochemical, physiological, and developmental evidence. We commend the authors for this effort to modernize the early working model of Langley (1903) and to incorporate the overwhelming evidence that afferent signaling to the nervous system for the purpose of autonomic regulation is commonplace. It is probably unnecessary to classify afferents according to their potential efferent influences, and in fact such classification can create confusion rather than clarity. We consider a classification that relies strictly on describing the functional information transduced and delivered to the central nervous system (CNS) to be sufficient; this general principle should be expanded beyond primary afferent neurons to include a far wider range of cells that secrete signal molecules that impinge on the nervous system.

First, afferents should not be classified according to a possible efferent outcome because such outcomes can overlap and can depend on the organism's past experience and the context of the stimulus. A "somatic" stimulus (nociception) may evoke a conscious perception, a somatic reflex withdrawal, and a change in blood pressure and heart rate. An auditory stimulus may evoke a reflex somatic head movement, an autonomic startle response, and conscious processing of information content. Stretching a hollow viscus may evoke not only autonomic responses but contraction of somatic muscles, as occurs in "guarding reflexes" in appendicitis. Any attempt to categorize these afferents as somatic or autonomic, when they can clearly evoke both types of responses, is futile. Afferent signals are also interpreted in the context of past experience. Virtually any sensory stimulus, including immune-derived chemical signals, can evoke a conditioned somatic or autonomic response, or both, depending on past learning and associations (Ader & Cohen 1985).

Afferent signaling can clearly be processed through very complex reflex, cerebellar, and lemniscal channels (Nauta & Fertag 1986). The parcellation of afferents into somatic or autonomic categories is artificial. Most behaviors, such as eating, reproducing, or walking, require highly integrated regulation of lower motor neurons, preganglionic autonomic neurons, and neuroendocrine outflow. Afferents are only one of many contributing signals that coordinate such behaviors. It is equally doubtful that any target organ in the periphery is supplied by afferents and efferents related only to somatic or autonomic activities. Skeletal muscle itself depends on autonomic efferents for the control of its blood supply. The threshold of some sensory receptors can be regulated by adjacent postganglionic sympathetic noradrenergic endings (Lowenstein 1956; Pierce & Roberts 1981; Roberts & Levitt 1982). In some species, such as the cat, the pancreas and visceral organs possess an abundance of pacinian corpuscles and large myelinated axons. Even the bone marrow possesses large myelinated axons (Lichtman 1981); we do not agree with P & P that it is supplied exclusively by B-afferents and autonomic efferents. As the authors note, many afferents, such as substance *P* unmyelinated fibers, can secrete their transmitter locally from the peripheral arborizations and alter autonomic functions (including immune functions), somatic functions, or both, regardless of the central connections of these afferents (Goetzl et al. 1988; Payan & Goetzl 1987). Furthermore, it does not seem necessary to create an artificial efferent category of "homeostatic" activities and try to fit afferent contributors into a new and even broader category. Virtually any afferent can be considered a contributor to "homeostatic activities." Ia muscle spindle afferents help to restore acutely stretched muscle length to a centrally determined set point, thus restoring homeostasis.

Perhaps B-afferent neurons share structural or developmental similarities with each other, but it is dangerous to hypothesize functional similarities on these criteria. Cells that look alike histologically in the parvocellular paraventricular nucleus of the hypothalamus can be subdivided into a dozen or more functional groups with different projections (Swanson & Sawchenko 1983). Cells that are similar histochemically may have widely divergent functions and projections, brain stem noradrenergic neurons, for example (D. Felten & Sladek 1983). B-afferent neurons and autonomic postganglionic neurons may both respond to nerve growth factor (NGF), but so do central cholinergic neurons of the basal forebrain (Hefti 1986; Williams et al. 1986). It is also abundantly clear that individual peripheral nerves and central tracts can carry axons subserving a multiplicity of functions, and that central nuclei and autonomic ganglia can contain anatomically homogeneous neurons subserving many functions. In addition, ontogenetically similar birthdates do not predict similarity of function.

We are left with physiological function as the best choice for describing heterogeneous populations of neurons or axons. Any attempt to categorize afferents by potential involvement in a specific efferent context several to dozens of synapses away will confuse the real issue, which is "what information does a primary afferent transduce and convey to the CNS?" We feel that the current concept of "afferents" as limited to primary sensory neurons is far too restrictive, and should be expanded to include other cells whose signal molecules reach the CNS and evoke somatic, autonomic, or neuroendocrine responses. Cytokines from immunocytes can evoke central neuronal responses, particularly in the hypothalamus (Besedovsky et al. 1983; Berkenbosch et al. 1987); they can also alter the secretion of norepinephrine from sympathetic postganglionic nerve fibers (Besedovsky et al. 1979) that directly innervate immunocytes in the parenchyma of lymphoid organs (D. Felten et al. 1987a; 1987b; S. Felten et al. 1988). Some lymphocytes can synthesize and secrete classical neuropeptides (Blalock 1984; 1979). Such cells may act functionally as "mobile afferents." Hormones from the periphery can evoke central neuronal activity by receptor mediated mechanisms (Reul & deKloet 1985). In addition, autonomic efferents supply a far wider range of target tissues than previously thought, including innervation of metabolic cells such as hepatocytes (Fuller et al. 1981) and brown fat (S. Felten et al. 1986; Himms-Hagen 1984) and direct contacts with lymphocytes and macrophages (S. Felten & Olschowka 1987; S. Felten et al. 1988). Signaling by neurotransmitters, cytokines, and hormones may therefore share many functional characteristics, including their ability to report events to the CNS from the internal or external periphery, to evoke neuronal activity, and to influence somatic, autonomic, and neuroendocrine efferent responses of the nervous system (D. Felten et al. 1987b; 1989). The cells secreting these signal molecules should all be

considered primary afferents from a functional viewpoint and should be categorized according to the information they transduce and convey, not the multiplicity of effector responses to which they may eventually be able to contribute. Let afferents be afferents.

B-afferents: The basis for autonomic reflexes?

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In this target article, Prechtl & Powley (P & P) present an argument based on morphology, histochemistry, and ontogeny for considering the B-afferents as a distinct population whose functional role is homeostasis. It is this functional aspect that I wish to emphasise in my commentary.

The hypothesis for the B-afferents is set in an historical context by suggesting that they fulfill the category of autonomic afferent that Langley (1921) failed to define because, as P & P propose, he did not have access to present-day markers. Indeed, P & P go so far as to conjecture that if Langley had had access to today's data, he himself would have assigned B-neurones to the autonomic afferent category. However, even with modern morphological and histochemical techniques, one still has the problem that autonomic responses are often linked to somatic events and do not always go unperceived. As P & P themselves point out, this is contrary to Langley's definition of an autonomic afferent.

One can develop this theme further by considering the afferent innervation to an organ such as the stomach. The peripheral fields of afferents can be identified and mapped out, and the course of the afferent fibre can be followed through the vagus nerve to a cell body in the nodose ganglion and on into the brain stem. This is clearly a candidate for an autonomic afferent; however, the argument fails when one considers the consequence of its stimulation. It may indeed give rise to autonomic reflexes but it could also evoke behavioural responses like satiety and somatic events like vomiting; it could also mediate sensations like gastric fullness or nausea (Andrews 1986). The same would be true for an afferent ending supplying the same target but traveling via the splanchnic nerve to the dorsal root ganglion. The activation of these afferents, however, would give rise to a different subset of autonomic and somatic responses and to different sensations, most probably pain.

Nodose and dorsal root ganglion cells clearly differ on functional grounds. Putting aside these differences for a moment, however, one can indeed identify a number of common features. Both afferents have unencapsulated "bare" nerve endings and unmyelinated axons and both activate autonomic responses that can be considered homeostatic. In this respect, a wide range of mechanical and chemical sensitivities have been described in these afferent endings (Grundy 1988). In addition, a feature that sets these afferents apart from the encapsulated sensory endings is their efferent role resulting from the release of peptide transmitters and modulators from stimulated nerve terminals or after antidromic invasion of axon collaterals (see Dockray 1987). These afferent endings may therefore mediate local responses while simultaneously providing the central nervous system with afferent information relevant to the characteristics of the stimulus. It is presumably this efferent function which is reflected in the morphological and histochemical features of the cell bodies that distinguish these afferents from the purely sensory ones.

Although I disagree with P & P's supposition that it was the B-afferents Langley was looking for by way of autonomic afferents, I have some empathy with the view that two cell types predominate in the dorsal root ganglion with the B-afferent providing the unmyelinated C-fibres (here the terminology starts to get cumbersome), which serve not only afferent functions but, through axon reflexes, also efferent functions. To consider the B-afferents a fundamental division of the peripheral nervous system, however, it is essential that the hypothesis incorporate the cranial nerves. Here the argument is weakest. Of the afferent fibres running via the vagus nerve we are informed (section 2.3) that the jugular ganglion is the cranial counterpart of the dorsal root ganglion. Most of what we know about vagal afferents, however, arises from studies on the nodose ganglion, excluded from the B-afferent classification, yet containing cell bodies with unmyelinated axons terminating in bare nerve endings and transporting bioactive peptides towards the periphery. Nodose and dorsal root ganglion cells differ also in morphology and electrophysiology (Stansfield & Wallis 1985). The cell bodies with unmyelinated afferents in the nodose are referred to as C-neurones but are undoubtedly involved in homeostatic regulation. If there are non-B-afferents involved in homeostasis and B-afferents not involved in homeostatic mechanisms, then the classification becomes unwieldy.

"What's in a name?"[1] A case for redefining the autonomic nervous system

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For Juliet (Harrison 1968), nomenclature was not an impediment to her understanding of either roses or Romeo, because she had formed an adequate operational definition of both. Scientists are seldom so fortunate. Of necessity, we work much like the blind men who attempt to organize a variety of separate observations into an acceptable definition of an elephant. The result is that scientific definitions can be operationally inadequate and can generate more confusion than clarification. The present report by Prechtl & Powley (P & P) seeks to complete and refine Langley's (1903) definition of the autonomic nervous system. This commentary proposes that Langley's autonomic nervous system concept is flawed[2] and should be reconsidered using physiological criteria as a foundation.

P & P offer some interesting insights into the phenotypic, ontogenetic, and functional similarities between B-afferents and autonomic neurons. They hypothesize that B-afferents represent the afferent limb of the autonomic nervous system that Langley (1903) proposed but could not document anatomically. Although this hypothesis has merit, it does not completely resolve Langley's dilemma. P & P's autonomic B-afferents constitute a subset of the B-afferent population and are distinguishable only on the basis of direct functional and synaptic influence on autonomic tissues and neurons. Consequently, one finds oneself positioned between Herrick (1922), and Dart (1922), trying to decide just what constitutes a visceral (i.e., autonomic) structure or function versus a somatic one. What is worse is the need to parcellate so-called autonomic and somatic actions mediated by the same B-neuron. In considering this target article, I concluded that a reformulation of the concept of the autonomic nervous system might be more productive than attempting to fit modern neurobiological data into the Procrustean bed of Langley's definition. I would therefore like to propose an alternative definition of the autonomic nervous system.

The basis for redefining the autonomic function is a holistic view of the nervous system. Although the nervous system is clearly a heterogeneous structural and functional entity when considered in detail, it can be viewed simply as an entity composed of input, integrative, and output components. Func-

tionally, the nervous system accomplishes homeostatic regulation and volitional activity, but these functions do not form mutually exclusive categories. In this simplified organization of the nervous system, the autonomic nervous system would comprise those neurons that participate in nonvolitional, stereotyped behaviors (viz., reflexes) for the purpose of homeostatic regulation (Mountcastle 1980).

This alternate perspective of the autonomic nervous system is clearly very broad and would include functions that would probably be questioned by students of the autonomic nervous system. The scheme proposed above, however, does provide a parsimonious definition of a biological system charged with maintaining homeostasis. Furthermore, the validity of this definition does not rely on phylogenetic, ontogenetic, or phenotypic considerations of either the neurons or target tissues. One merely identifies the stimulus and response and those afferent and efferent nerves that constitute the reflex arc. For example, if Langley had considered thermoregulation in the skin physiologically rather than anatomically, thermoreceptive nerve fibers would obviously constitute the afferent limb of the reflex despite their lack of a unique histologic identity. Furthermore, the similarity in the dorsal horn distributions (laminae I and V) of fine fibers labeled from a splanchnic nerve (Cervero & Connell 1984) and those labeled from the gastrocnemius-soleus muscle (Craig & Mense 1983) suggests that homeostatic function is a more accurate criterion for including neurons in the autonomic nervous system than the classification of the target structure as either somatic or visceral (Kuntz 1953).

In summary, a concept of the autonomic nervous system based on functional criteria and supported by structural data would be less confusing than the present definition, which is primarily constructed from anatomical observations and classifications.

NOTES

1. William Shakespeare, *The tragedy of Romeo and Juliet*, Act II, Scene ii.

2. Langley's (1903) decision to attempt the classification of autonomic afferents using only anatomical criteria ignored Flourens's (1842) famous caveat that, "anatomy without physiology is anatomy without purpose."

Convergence of autonomic afferents at brain stem neurons: Stomach reflex and food intake

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The animal body is often viewed as consisting of two distinct parts: a visceral and a somatic one. The former contains the homeostatic apparatus related to the regulation of various parameters of the internal environment. The latter contains the apparatus related to the processing of inputs from the external environment and to the control of skeletomotor activities that result in altering the external environment of the organism. The two are thought to have evolved in parallel and become welded together to form an organism, each with its unique afferent and efferent systems. However, the afferent system of the visceral part has been relatively ignored. Prechtl & Powley's target article aims to distinguish the autonomic afferent system by arguing that many of the sensory neurons known as B-neurons are specifically dedicated to the visceral functions.

The autonomic system is conceptualized around its function of keeping "harmony" and "sympathy" among visceral functions. The maintenance of harmony is attributed to negative feedback and balance between the sympathetic and parasympathetic controls. However, how the motor output is controlled by various afferents is not well delineated. Anatomically, the afferent portion of the visceral nerve is substantial. It is estimated that 90% of the abdominal vagus and 10 to 20% of the greater splanchnic nerves are afferent fibers in the cat (Agostoni et al. 1957; Andrews 1986; Kuo et al. 1982). Mechanosensitive and chemosensitive endings exist in the gastrointestinal wall and the signals are conveyed by the vagus (Barber & Burks 1983; 1987; Barber et al. 1987), splanchnic (Ranieri et al. 1973), and other nerves (Kreulen 1984; Kreulen & Peters 1986) to the ganglion and central nervous system. Recent studies on autonomic afferent activities and their convergence are reported here to complement the target article and point out the importance of afferent convergence to homeostatic behavior. The studies involved intracellular and extracellular recordings from the inferior mesenteric ganglion (IMG) and the medial subnuclei of nucleus tractus solitarius (NTS) in response to electrical stimulations of sympathetic and parasympathetic branches innervating various areas of the gastrointestinal tract.

Keef and Kreulen (1988) showed in guinea pigs that simultaneous applications of submaximum stimulation to the lumber colonic and splanchnic nerves led to a summation of slow excitatory postsynaptic potentials recorded at IMG neurons, indicating a convergence of input from those sources. Barber and Yuan (1989a) stimulated the ventral gastric vagal branch and its major and minor branches one at a time or simultaneously in 16 cats. They found that 159 NTS cells responded with a mean conduction velocity of about 1 m/sec, and 42% showed a convergence when two branches were stimulated simultaneously. Barber and Yuan (1989) also stimulated the gastric branches of ventral and dorsal vagal trunks and left the greater splanchnic sympathetic nerves in 12 cats. Among the 265 NTS cells that responded to gastric vagus stimulations, 43 were completely or partially inhibited by simultaneous stimulation of the splanchnic nerve. The inhibitory effect of splanchnic input lasted for 30 seconds following termination of stimulation. In addition, 3 vagal units were also activated by greater splanchnic input alone. Yuan and Barber (1989) stimulated the gastric branches of dorsal and ventral vagal trunks in 12 cats. Among the 153 NTS units found, 95 were evaluated for convergence of inputs. A total of 19 units showed convergence of ventral and dorsal vagal inputs, 14 with excitatory and 5 with inhibitory effects. Barber et al. (1989) stimulated the proximal gastric vagal branches of dorsal and ventral vagal trunks in 31 cats. Among the 406 responding NTS units found, 163 were from stimulations of the branches of the ventral vagal trunk, 170 from stimulations of the branches of the dorsal vagal trunk, and the remaining 73 responded to stimulations of the branches of both vagal trunks. An excitatory or inhibitory convergence of the inputs was found in 41% of the units.

Convergence indicates an integration of neuronal activities from different sources which eventually controls the output to achieve harmony among various functions. How the afferent signals converge to determine the autonomic output, however, is not clear. In the short run, homeostasis is maintained by various reflexes, but ultimately it must be supported by the external resources (e.g., food and water) obtained via skeletomotor behavioral means. So, studying convergence within the visceral or somatic part and convergence between the two parts may further the understanding of how harmony within an organism is achieved by the organism's interactions with its environment.

Gustatory afferent pathways have been well traced (Norgren 1976; Norgren & Leonard 1973; Pfaffman et al. 1979) and systematic tracing of gastrointestinal afferent pathways has recently begun. Gustatory and vagus inputs are known to interact with each other such that an additive convergence occurs between the evoked spikes of gustatory and vagus stimulations in a certain parabrachial nucleus region in rats (Hermann & Rogers 1985). Thus, somatic taste information, on its way to higher brain areas, may be modulated by visceral vagus input, and, conversely, information on visceral states may be modified

by gustatory input. Hermann and Rogers (1985) state that the presence of a vagal afferent "background" on a population of parabrachial neurons may increase the sensitivity of these neurons to parallel gustatory input.

Water intake can be affected by vagotomy (e.g., Zimmer et al. 1976), but whether the effect involves afferents or efferents has not been studied. Saline solution applied to the tongue of sodium-deprived rats is known to evoke much less activity than in normal animals in the chorda tympani fibers (Contreras & Frank 1979). The sodium-depleted state may involve a vagal afferent tone affecting gustatory sensitivity via a centrifugal pathway. A gut peptide, cholecystokinin, has been shown to induce satiety in food intake mediated by the gastric vagus afferent (Smith et al. 1981) and NTS in rats (Crawley 1985). Whether the peptide effect involves taste input or the control of ingestive responses has been investigated by recording chorda tympani activity and the response in rats, of licking milk with somewhat ambiguous results (Gosnell & Hsiao 1984; Hsiao & Spencer 1983).

Vagal inputs and their convergence were further traced to the lateral hypothalamus, parabrachial nucleus, area postrema, and ventral tegmental nucleus (Yuan, personal communication), the areas where intake regulation and taste hedonic reactivity may be mediated. Whether the vagal and taste afferents might converge at those areas, however, has not been studied. Information regarding the interaction between visceral and somatic afferent activities at various level so the brain could reveal control mechanisms for behaviors related to homeostasis.

B-afferents: A system of capsaicin-sensitive primary sensory neurons?

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In their target article, Prechtl & Powley (P & P) claim to have identified a "missing" population of "autonomic afferents" sought in vain by Langley (1921). In this commentary, I would like to present evidence that B-afferents comprise a unique population of primary sensory neurons that is capsaicin-sensitive, show marked anatomical and functional heterogeneity, and essentially fail to match the proposed class of autonomic afferents.

Capsaicin-sensitive primary sensory neurons (CPSNs) coincide with the population of type-B neurons located in spinal and cranial sensory ganglia (see, e.g., Jancsó et al., 1977; Nagy 1982; Fitzgerald 1983; Buck & Burks 1986; Lawson 1987a). Henceforth, it is reasonable to assume that "B-afferents," as defined by P & P, are essentially identical to capsaicin-sensitive afferents (see also Kai-Kai 1986). The existence of an anatomically distinct system of CPSNs innervating a wide variety of organs and tissues, and a classification of these neurons with respect to their function and the type of tissue they innervate, have recently been proposed (Jancsó et al. 1987). Accordingly, somatic and visceral afferents with "sensory afferent" function (i.e., transmission of sensory, mostly nociceptive impulses to the central nervous system) or "sensory efferent" function were distinguished. The latter is a salient, distinctive feature of many capsaicin-sensitive afferents exerting local effector or regulatory functions via the release (secretion) of neuropeptides from their peripheral terminals (for reviews, see Szolcsányi 1984; Maggi & Meli 1988; Holzer 1988; see also Szolcsány's accompanying commentary, this issue). The unique "sensory efferent" or "secretosensory" nature of CPSNs has been clearly demonstrated in experiments showing that the soma and the peripheral branch of these ganglion cells may represent an independent functional entity capable of responding to environmental stimuli with local vascular and inflammatory responses unrelated to the mediation of afferent messages towards the central nervous system (cf. Jancsó 1981; Lembeck 1983).

P & P suggest that type-B primary sensory neurons meet the criteria of autonomic afferents. However, P & P do not set such criteria; hence a clear definition of autonomic afferents is not given. Several traits of B-afferents, however, are apparently not in keeping with the hypothesis that they are autonomic afferents.

The notion that "the role of B-neurons in skeletomotor and behavioral defensive reflexes is functionally and synaptically less direct" and "only autonomic neurons and autonomic effector tissues have been shown to be directly driven by B-neurons" (sect. 4.1, para. 6) is not tenable in the light of the numerous behavioral and electrophysiological studies showing the crucial role of these afferents in somaesthetic mechanisms, including pain (cf., e.g., Buck & Burks 1986; Chung et al. 1985; Fitzgerald 1983; Jancsó et al. 1977; 1987; Otsuka et al. 1982; Szolcsányi 1984). Indeed, a substantial population of B-afferents has been shown to represent cutaneous polymodal nociceptor afferent fibers (Lynn & Carpenter 1982; Szolcsányi et al. 1988). The designation of these afferents as autonomic would clearly lead to much confusion. Moreover, although stimulating these cutaneous afferents may lead to a variety of autonomic responses, it is to be noted that similar reflexes can be elicited by non-noxious stimuli that excite receptors with A-afferents (cf. Sato & Schmidt 1987). These findings are in line with Langley's (1903) suggestion that afferents cannot be classified solely on functional grounds.

The central projection patterns of B or capsaicin-sensitive somatic and visceral primary afferent fibers have been shown to be characteristic and distinctly different (cf. DeGroat 1986; Fyffe 1984; Jancsó & Maggi 1987). Therefore, application of a new, unifying taxonomy to these substantially different types of primary afferent neurons seems to be equivocal.

These findings provide only a few reasons for casting some doubt on the validity of the proposed classification of B-afferents as autonomic. However, B-neurons obviously represent a unique, although anatomically, functionally, and neurochemically heterogeneous population of capsaicin-sensitive primary afferent neurons. Available experimental evidence indicates that there are three main categories of B-type, capsaicin-sensitive primary afferents. These include (1) nociceptive and thermal, (2) reflex, and (3) regulatory afferents.

The first class consists of Aδ mechanonociceptor, C polymodal nociceptor, and possibly warmth receptor afferents, which are involved in the transmission of impulses elicited by noxious or thermal stimuli. Furthermore, polymodal nociceptors play a decisive role in the mechanisms of antidromic vasodilatation and neurogenic inflammation (see, e.g., Chahl 1988; Jancsó 1966; Jancsó et al. 1977; Obál et al. 1987; Szolcsányi 1984; Szolcsányi et al. 1988).

The second class consists of various visceral afferents involved in the mediation of cardiovascular and respiratory reflexes. Presumably only this small subpopulation of B-neurons is intimately associated with a classical autonomic reflex function. In addition, B-afferent axon collaterals to sympathetic ganglia may also initiate or modulate autonomic reflexes without the recruitment of central nervous circuits (Matthews & Cuello 1982).

The third class consists of visceral afferents involved, inter alia, in the local regulation or modulation of vascular, inflammatory (Jancsó et al. 1980), and immune (Payan et al. 1984) responses via the release (secretion), from their nerve endings, of neuropeptides, most known to be regulatory peptides. Reflex action, except for axon reflexes, which are of decisive importance, is not a characteristic feature of these afferents, for they exert their local effector or regulatory effects mostly without the contribution of the central nervous system. The function of these regulatory afferents displays little resemblance to that of afferents that could be designated as autonomic. It is interesting

to note, however, that many B-afferents have certain common features with autonomic efferents, for they innervate vascular and visceral smooth muscle and cardiac muscle, where they exert an effector function (cf. Holzer 1988; Maggi & Meli 1988).

In conclusion, although the hypothesis put forward by Prechtl & Powley is an attractive one, at present it has little firm theoretical or experimental support. Future research will show whether the similarities between autonomic postganglionic and B primary afferent neurons described in the target article are only incidental or whether experimental findings can indeed indicate a fundamental association of the autonomic nervous system with any special division of the sensory system.

Network-structure of the peripheral autonomic innervation apparatus should be thoroughly evaluated

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In the target article, Prechtl & Powley (P & P) have persuasively concluded that B-neurons of the dorsal root ganglion represent the afferent divisions of the autonomic nervous system that Langley (1921) had searched for, but failed to find. If Langley had had access to the histological, physiological, and pharmacological data now available, however, he would surely have accepted this conclusion. Why could Langley not find the afferent divisions of the autonomic nervous system? I would like to suggest a reply based on our recent morphological studies on the network structure of the peripheral autonomic innervation apparatus and the so-called "interstitial cells of Cajal" (see Thuneberg 1982).

It is assumed that the osmium stain, which Langley used in his histological study, is not adequate to demonstrate the complicated structure of the visceral autonomic neurons and Schwann cells. Furthermore, Langley, like his contemporaries, was strongly influenced by Cajal (1911) who believed that there are interstitial neurons (cells) that are intercalated between the autonomic nerve terminals and effector cells. I feel Langley was therefore unable to escape from the neuron doctrine and to notice the network structure of the visceral autonomic innervation.

We have recently investigated various organs of the guinea pig (iris, ciliary body, ciliary ganglion, superior cervical ganglion, pancreas, small intestine, adrenal medulla, and carotid body) using modern light microscopic and transmission/ scanning electron microscopic techniques. Through light microscopy of Champy-Maillet (zinc iodide-osmium tetroide: ZIO)-stained tissue preparations, we have observed dense nerve networks consisting of a Schwann cell framework and neuronal projections in all the organs examined. Through scanning electron microscopy we have also revealed the three-dimensional architecture of the nerve networks. To make visualization of the cellular elements clearer, a digestion method, using concentrated sodium hydroxide (7.2 gm NaOH plus 30 ml distilled water) at 60°C for 14 to 16 min, was used. With this technique we could remove the collagenous and elastic fibers and basement membrane in the tissues so that the fine structure of nerve bundles was revealed (Figure 1).

Schwann cells projected several cytoplasmic processes that attached to each other and made a framework supporting the varicose and nonvaricose neuronal processes. A Schwann cell frequently ensheathed more than 10 neuronal processes. Varicose neuronal processes occasionally ran for more than 100 μm without a Schwann cell sheath. Transmission electron microscopy of the ultrathin sections of the glutaraldehyde/osmium tetroxide-fixed tissues revealed the ultrastructure of the nerve

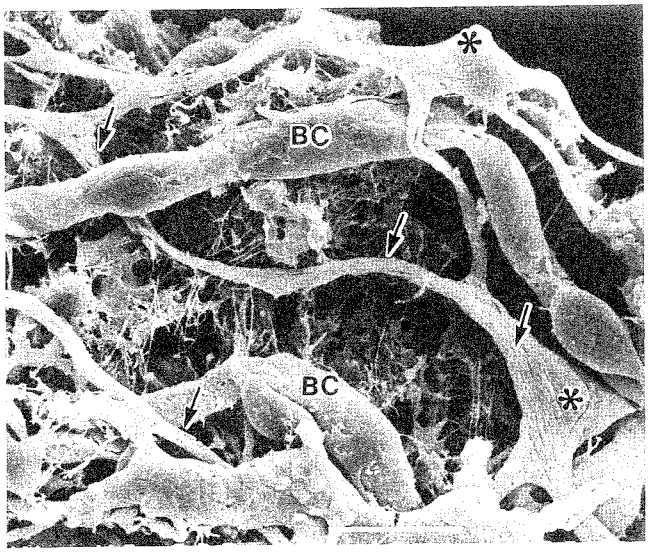

Figure 1 (Kobayashi). Scanning electron micrograph showing structure of the autonomic groundplexus in a villus of guinea pig small intestine. Arrows indicate bundles of varicose nerve terminals. Asterisks indicate Schwann cell. BC: blood capillary. Calibration: 10 μm.

fibers. Direct contacts between naked neuronal varicosities and effector cells, such as smooth muscle cells and glandular cells, were found. These results obtained from our recent morphological studies are consistent with the "autonomic groundplexus theory" proposed by Hillarp (1959). Thus, in the peripheral end, processes of the autonomic neurons, guided along the Schwann cell framework, probably converge into bundles that form a branching and anastomosing network (Figure 2). Based on the above information and findings it was apparently

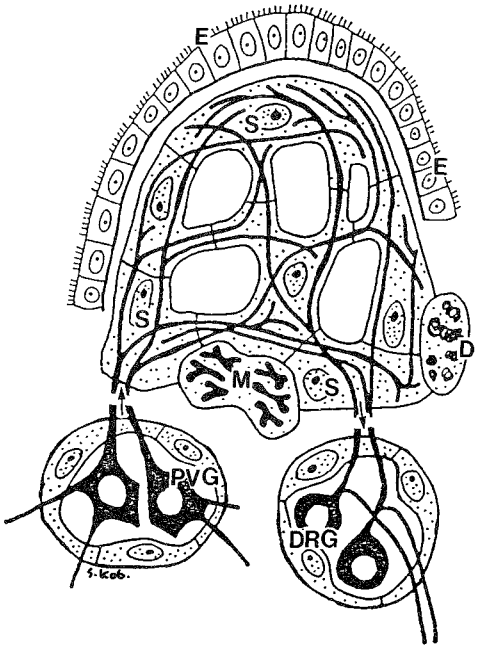

Figure 2 (Kobayashi). Schematic representation of the structure of the autonomic ground plexus. Nerve fiber bundles are ensheathed by a Schwann cell framework (S). D indicates a degenerating Schwann cell. DRG: ganglion containing B-afferent neurons. E: effector cell. M: mitotic Schwann cell. PVG: ganglion containing autonomic motor neurons.

impossible for Langley (1921), who used rather primitive histological techniques, to have demonstrated the exact histological architecture of the autonomic groundplexus and thus successfully identify the site of sensory perception of the autonomic afferent neurons in visceral organs.

It is not possible to deal with the historical development of the peripheral autonomic innervation concept in the twentieth century without considering the "interstitial cells of Cajal" (Thuneberg 1982). Cajal (1911) described a chain of peculiar nerve cells in the interstice between the smooth muscle and glandular cells in the intestine, pancreas, and other organs. He regarded the interstitial cells as primitive neurons, whose function would fall between the autonomic nerve terminals and the effector cells. Careful examination of Cajal's original description, however, has recently revealed that what Cajal described as interstitial cells are actually a composite of Schwann cells and neuronal processes of the autonomic groundplexus (Kobayashi et al. 1989). It is certain that with the techniques available then, Cajal could not differentiate Schwann cells and neuronal processes, hence he mistakenly regarded the composite structure as independent nerve cells. It is possible that Cajal's study of the network structure of the autonomic groundplexus was hampered by the prevailing preconceptions at that time. For Cajal who, contrary to the views of many reticularists, established the neuron doctrine, network formation in the innervation apparatus was apparently an inconvenient idea.

One of the unique merits of the autonomic groundplexus theory of Hillarp (1959) may be that it explains the network formation of the autonomic innervation apparatus without contradicting the neuron doctrine. It must be pointed out, however, that Hillarp considered the interstitial cells of Cajal Schwann plasmodium. He did not notice the independence of the individual Schwann cells; hence, he used the term "plasmodium." Furthermore, he did not see the neuronal processes that join with the Schwann cell in the "interstitial cells of Cajal"; thus Hillarp did not understand Cajal's misinterpretation concerning the "interstitial cells." We now know that the Schwann cells in the autonomic ground plexus are constantly produced by cell division to balance the dying cell population, whereas neuronal processes can elongate or recede along the track provided by the Schwann cells. Thus, the network structure is essential for the plasticity of the peripheral autonomic innervation apparatus (Kobayashi et al., in press).

What percentage of B-afferents actually come from the autonomic groundplexus? We still do not know. Are there specialized end organs such as mesenteric Pacinian corpuscles for some of the B-afferents? Such a sensory apparatus has not yet been demonstrated in sufficient numbers. There is a possibility that a large fraction of the B-afferents form free nerve endings. The most likely origin of the B-afferents, however, is the autonomic groundplexus, where they form a bundle with many neuronal processes. Although in the autonomic groundplexus processes of different neurons come together into a bundle running for a considerable distance in parallel, separated from each other by about 20 nm, it is still unclear whether or not interactions between these neurons may take place.

Our present view of neural transmission is mainly constructed from the data obtained in the neuromuscular junction of the skeletal muscle and in the synapses of the central nervous system. It seems inadequate to apply what we understood in the somatic nervous system directly to the peripheral autonomic nervous system, whose peripheral terminals are characterized by the formation of the autonomic groundplexus. This innervation apparatus seems more suitable for the rather diffuse stimulation of the effector cells seen in the autonomic nervous system than for the exact and restricted actions of those seen in the somatic nervous system. Because of its possible important role in the mechanisms of sensory perception in the visceral B-afferents, I feel that the network structure of the peripheral autonomic innervation apparatus should be thoroughly evaluated.

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Does form underlie function in the neural control of homeostasis?

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It seems that Prechtl & Powley (P & P) seek to answer three basic questions in their target article. The importance of these questions ranges from mildly interesting to extremely profound.

(1) "Are there afferent fibers in the autonomic nervous system?" This is a largely semantic issue, but one that has been a thorn in the side of students of the autonomic nervous system (ANS) for many years. As P & P point out, Langley's original formulation of the ANS was lopsided, providing no convenient way to refer to a class of neurons (i.e., visceral sensory) that was generally recognized as a valid fundamental neuronal subgrouping.

It is not clear that the B-afferent classification scheme does much to resolve this issue. Adopting this nomenclature gives us a new way of looking at a class of sensory neurons, but provides us with no guidance as to how we should refer to the nonsomatic component of the B-afferent population, which would still appear to be a group of sensory fibers in search of a name. This may well be an issue whose best solution lies in being ignored. To paraphrase Lewis Carroll, "The autonomic nervous system is whatever we say it is."

It is almost universally recognized that there are sensory neurons in, for example, the vagus nerve, which do not subserve "somatic" afferent function as it is generally conceived. Although it may not be in strict accordance with Langley's original asymmetrical formulation of the ANS, and may be considered somewhat socially unacceptable, these have become de facto "autonomic afferents." Whether that term is actually used to describe them, or a more convoluted euphemism meaning essentially the same thing, would appear to be a matter of personal preference.

(2) "Do A- and B-afferents form distinct populations of afferent neurons?" This is the point where P & P make their most cogent arguments. Using the dorsal root ganglion (DRG) as a model, they present a compelling case that somatic, sympathetic, and parasympathetic "afferents" can be partitioned into two largely nonoverlapping distributions based primarily on ontogeny, but also on the basis of histochemical characteristics, responsiveness to NGF, fiber type, receptor ending type, and the sensory modality subserved.

This hypothesis has been extensively documented in the DRG, but so far the data are somewhat sketchy concerning the extension of these principles to other neurons that would be considered B-afferents on an a priori basis, in particular, sensory neurons associated with the parasympathetic nervous system. P & P's somewhat abbreviated treatment of cranial nerve sensory ganglia does not give much information concerning, for example, whether the placode-derived distal ganglia of cranial nerves will fit into their classification scheme.

A little information on the levels of RT-97 binding and arginine vasopressin content (apparently the sine qua non of A- and B-neurons, respectively) of these presumptive A-afferents in the nodose, petrosal, and distal trigeminal ganglia will go a long way toward indicating whether this A/B dichotomy represents a fundamental anatomical (and, one would hope, func-

tional) property of the nervous system, or merely an interesting phenomenon peculiar to the DRG.

(3) "Do A- and B-afferents represent general classes of functionally distinct groups of neurons?" It is this question, naturally the one for which there are the fewest available data on which to base a conclusion, that would provoke the greatest change in our ways of conceptualizing the organization of the nervous system.

The idea of a group of ontogenetically and anatomically distinct set of neurons concerned exclusively with homeostatic function is certainly extremely attractive. The strongest evidence in favor of this concept available to date seems to be the parsimony gained by considering "substance P/B-afferents" as a functional group, even though some of them are traditionally labeled "somatic" afferents and some are "visceral" afferents. However, given that (1) substance P-containing neurons afford only partial representation of the B-afferent class and that (2) P & P provide no evidence that *only* B-afferents contain substance P, it would seem prudent to judge this as tentative.

P & P slip into using "substance P-containing" and "capsaicin-sensitive" almost as synonyms for B-afferents, and this makes the notion of B-afferents as a functionally related class of neurons partly a self-fulfilling prophecy. Inasmuch as some neurons that would not appear to be B-afferents according to the present scheme (e.g., nodose ganglion; Ritter & Dinh 1988) are capsaicin-sensitive, this implied isomorphism may be leading us down a garden path.

Clearly, considering nociceptive sensory neurons as a separate class has heuristic value; the fact that these neurons bridge other classification schemes points out the inadequacy of these schemes. How well other sorts of "homeostatic" sensory fibers such as those innervating intestinal, hepatic, and vascular chemoreceptors, and so forth, fit into this phylogenetic and ontogenetic dichotomy will determine how well this grouping can serve as a template for sensory nerve function.

Visceral, autonomic, or just plain small dark neurones?

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Prechtl & Powley (P & P) have put forward the proposition that B-neurones are those sensory neurones dedicated to autonomic function. They suggest, however, no specific criteria for distinguishing the afferents that are involved in autonomic function. I shall therefore intend to discuss the relationship between B-neurones and visceral afferents that run with autonomic nerves because these presumably form at least a part of the neurone group with autonomic function. I shall classify skin and skeletal muscle as somatic structures for this purpose. Although some skin and muscle afferents may have effects on the autonomic nervous system, it is not easy to identify which ones. Part of this commentary will relate to whether neurones have A-fibres or C-fibres. I shall therefore use the terms "light" and "small dark" neurones (referring to the size and staining characteristics of the somata) rather than the terms A- and B-neurones respectively. The latter terms can be confused with the terms A-fibre and C-fibre. There is no space to take up particular points from the target article, so I shall address myself to a few of the broader questions raised.

Fundamental differences between light (A) and small dark (B) neurones? It seems clear that small dark neurones of dorsal root ganglia (DRGs) are indeed a fundamental subdivision of the primary afferent neurones, in terms of their cytology, development, cell size, distribution, and neurofilament content (e.g., Lawson & Biscoe 1979; Lawson et al. 1984). Using RT97, an antineurofilament antibody (Lawson et al. 1984) as a light cell marker, we have shown in rat DRGs that all A-fibre neurones (including A-δ) and possibly a few C-fibre neurones are part of the light population, whereas the small dark cell population seems to be exclusively C-fibre neurones (Lawson & Waddell 1985).

Apart from RT97, which labels exclusively the light cell population in the rat, no other markers reproducibly distinguish the entire small dark population from the light population. Some of the markers listed in this context in P & P's article may not prove to be exclusively contained in the small dark cell population, because cell size per se is an inadequate indicator of cell type, as the size distributions of the light and small dark neurones overlap. For instance, substance P-like immunoreactivity (SP-LI) is in both the light (RT-97 positive) and small dark cell populations and in neurones with both C- and A-fibres (McCarthy & Lawson 1989). Unfortunately, we have failed to obtain any clear neuronal labeling with the same anti-arginine vasopressin antibody as that used by Kai-Kai et al. 1986 (see target article), one of two markers that P & P suggest would label the entire B-cell population. The other marker listed as labeling all B-cells in P & P's Figure 3 is myelin-associated glycoprotein, which is reported in chick DRG neurones only at an early stage in development. Even the neurotoxin capsaicin, which eliminates most small dark neurones and sensory C-fibres when given to neonatal rats, also causes the death of some light neurones and their A-fibres (Lawson 1987b). Thus, the lack of neurofilament is so far the only reproducible "marker" for the whole small dark cell population in adult animals that I know of, and this has only been demonstrated so far in the rat and mouse.

Can somatic and visceral afferents be distinguished? Afferents that travel along autonomic nerves can be retrogradely labeled and their characteristics can be studied. In the studies so far, no clearcut label has yet been found that can unequivocally distinguish between these neurones and those retrogradely labeled along skin or muscle nerves. Although CGRP-LI is found in a very high proportion of splanchnic visceral afferents (Molander et al. 1987), it is found in some skin and muscle afferents as well.

Somatostatin was one of the markers of B-cells suggested in the target article. However, this is found only in skin and muscle afferent neurones, not in splanchnic afferents (Molander et al. 1987), which again must argue against all B-cells being visceral afferents.

Could small dark neurones be exclusively visceral afferents? Although most visceral afferents have small somata, in retrograde labeling studies along the splanchnic nerve in the cat (Cervero et al. 1984) and the rat (Perry & Lawson, in preparation) only about 6% of the total number of lower thoracic DRG neurones were labeled, and these included mainly small but some medium and large neurones. This total number is only about 10 to 20% of the small dark cell population (which in the rat comprises 50 to 70% of the DRG). Recently we (Perry & Lawson) have found that about 25% of splanchnic afferents are RT-97 positive, that is, light neurones (and likely to be myelinated). Thus, not only are the visceral afferent neurones considerably fewer than the small dark neurones, but they include a substantial proportion of light neurones, providing little justification for equating small dark, B-neurones either specifically or exclusively with visceral afferent function.

The general differences in sensory function between C- and A-fibre neurones are well known and do not contribute to the argument for reclassification because C- and A-fibres project to both visceral and somatic structures. Thus, even if it were argued that the C-fibres to skin were autonomic in their function, A-fibres projecting to viscera make untenable a classification of C-fibre neurones as being exclusively autonomic/visceral and A-fibres as being exclusively somatic.

Would such a change in classification be an improvement? Although it seems clear that the small dark neurones, or B-

neurones, do indeed represent a major division of the peripheral nervous system, it seems equally clear from the above arguments that neurones in this subdivision are not exclusively those that project to visceral organs along the autonomic nerves. Whether they all serve some role in autonomic function remains an academic question because it is not clear how to identify afferents with autonomic function.

Unlike the motor system, which was classified by Langley nearly 70 years ago into autonomic and somatic using a variety of criteria, the sensory system has at present no clear anatomical, pharmacological, or histochemical methods of identifying visceral and/or autonomic afferent somata. A reclassification at this stage would therefore be very premature and would create unnecessary confusion. Until adequate information is available I feel we should stick to classification on the basis of something that can be used to identify the neurones, such as appearance and size (e.g., light and small dark neurones), and that we should continue to correlate these with conduction velocity, immunocytochemistry, and sensory and effector functions of the neurones. It is from studies such as these that further useful classification(s) may emerge.

Classification of peripheral neurones

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The great merit of Prechtl & Powley's (P & P's) target article on afferent neurones is the proposal for a functional unification of B-type neurones. This proposal is well founded on morphological, physiological, and ontogenetic criteria; its presentation in a historical context is appreciated. This commentary is in agreement with P & P's views and offers an extension of their classification based on pharmacological investigations, especially those recently performed in our laboratory. This classification is presented hierarchically and introduced by some special remarks.

Peripheral neurones are classified as efferents or afferents that are frequently encountered as a bundle of fibres commonly referred to as a nerve. Efferent nerves are not considered in the following classification and afferent connections from sensory organs, such as the eye or ear, are also excluded.

Primary afferent neurones are distinguished according to three criteria describing (1) morphological, (2) functional, and (3) neurochemical differences:

(1) Afferents are found either as somatic mixed or pure sensory afferent nerves. In addition, a considerable number of afferent C-fibres are found within autonomic nerves that are named according to their *efferent* functions, although some of them contain more than 50% afferents. Histologically, they are differentiated according to their diameter and myelinization, the type of vesicles they contain, their cell type (e.g., A or B) and the emergence of their fibres (unipolar or pseudounipolar); they are also defined by transmitter histochemistry or by specific enzymes.

(2) Afferents can be differentiated functionally (a) on the basis of considerable differences in conduction velocities between A- and C-fibres, (b) according to the specific type of information they convey, for example, from baroreceptors, chemoreceptors, stretch receptors, arising from the stimulation of either free-nerve terminals (C-fibres) or encapsulated receptors (Aδ- or Aβ-fibres), and (c) by their ability to evoke specific sensations (e.g., cold or pain) or reflex responses (salivation).

(3) Afferents are neurochemically classified according to their transmitters, which can be amino acids, peptides, purines, and other as yet unknown compounds.

An additional classification is derived from the effects of capsaicin. Capsaicin in very small doses has been found to stimulate peptidergic afferent C- and some Aδ-fibres specifically to impair their functioning for a long time, and even to cause their degeneration after a very large dose. The effect of capsaicin is specific to a population of primary afferent neurones that contain, in addition to substance *P*, several other peptides, some of which coexist in the same neurone. Capsaicin-sensitive fibres also contain a specific "fluoride resistant" acid phosphatase and purines. Their further differentiation and functional representation is under investigation.

The neurochemical classification of neurones according to their neurotransmitters was initiated by Dale's (1933) introduction of the terms adrenergic and cholinergic. The definition was based on the use of specific receptor blockers and was therefore preferred by pharmacologists. The initial distinction between muscarinic and nicotinic cholinergic as well as adrenergic receptor blockers was continuously elaborated in the meantime. A considerable number of receptor subtypes of neurones and peptides serves as some kind of pharmacological championship at present. The number of receptor types vies with the variety of transmitters that can be released by nerve endings. The neurochemical classification of peripheral afferent neurones distinguishes among their different neurotransmitters, that is, between amino acids, peptides, and purines. Modern peptide chemistry has allowed the isolation of a considerable number of biologically active peptides; bioassays, radioimmunoassays, and immunohistochemistry have supplied ample information about their existence in afferent neurones; capsaicin has been the main pharmacological tool to elucidate their physiological role (see below).

Neurones in the central nervous system (CNS) and the enteric nervous system can be most easily classified according to their neurotransmitters. In contrast to capsaicin-sensitive peptidergic primary afferents, neurones that are located in the CNS or in the gastrointestinal tract and contain the same peptide are not "capsaicin-sensitive." The enteric nervous system was already regarded by Langley (1903) as a separate autonomic entity. The enteric and the central nervous systems have in common the presence of several further neurotransmitters that do not occur in peripheral nerves, such as dopamine, serotonin, glycine, GABA, and enkephalins. The terms "efferent" or "afferent" can be applied to only part of the CNS, mainly the spinal cord. Concerning the neuronal connections in the enteral nervous plexus, the terms "oral" and "aboral" are used.

According to Cannon (1926), the basic function of the autonomic nervous system is to bring about the internal adjustment on which this constant state depends, that is, homeostasis. In addition, homeostasis is regulated by purely endocrine mechanisms independent of neuronal systems. In higher organisms, homeostasis is far more than the protection of the *milieu intérieur*, in the sense of Claude Bernard (1878/79). It encompasses adaptation to rapidly changing and often hostile environments as well as the propagation of the species. Rapid relay of information to regulatory centers is essential for immediate action and adequate adaptation.

Several endocrine regulatory functions are under additional neuronal influences. These might stem from the cortex or the limbic system or hypothalamic centers; they may be evoked by emotional, cognitive, or sensory (light, sound) signals or they may be conveyed from the periphery to the CNS by primary afferent neurones. Ample information has been collected during recent years showing that these messages from the periphery are conveyed mainly via capsaicin-sensitive primary afferent neurones. They evoke reflexes and neuroendocrine regulatory mechanisms and reach consciousness only to a small extent. Their transmitters are substance *P* and other neuropeptides,

which are released not only at the central terminals to mediate afferent signals, but also from peripheral terminals upon stimulation. The peripheral release of neuropeptides can be regarded as "the first line of defence" under terms like the "nocifensor system" or "neurogenic inflammation."

The autonomic reflexes evoked by the release of neuropeptides from the central terminals of peptidergic afferent C-fibres correspond to those that Langley included in his first concept of the autonomic nervous system in 1903. As osmium did not stain unmyelinated C-fibres, to which most of the peptidergic afferent fibres belong, Langley abandoned his earlier assumption and described an "efferent-only" autonomic nervous system (1921). Only after the discoveries in the field of peptidergic neurotransmitters from 1953 onward could the basis be established for the afferent part of the autonomic nervous system, and consequently its link to reflexes and neuroendocrine regulatory mechanisms (Lembeck 1988). Reflexes initiated by peptidergic, capsaicin-sensitive, afferent C-fibres serve neuronally mediated homeostasis; their influence on endocrine regulations might be understood as a kind of booster effect, evoked under certain conditions for a limited time, in order to promote additional hormone release. All together, the capsaicin-sensitive afferents can be regarded as the sentries of a network of defense (Lembeck 1987).

These considerations led to an extended version of Prechtl and Powley's Figure 2 in the form of the hierarchical classification in the table that follows.

Table 1 (Lembeck and Bucsics). *Peripheral afferent neurones*

Definition: All neurones outside the CNS that conduct in central direction physiological stimuli, except those of sensory organs.

Classification according to

0.1 Transmitters
0.2 Neurone type (morphological/electrophysiological criteria)
0.3 Neurochemical markers/criteria
0.4 Function

Additional classification of afferents might be based on recent findings in molecular biology, such as the specific cell adhesion molecules (CAMs) described by G. M. Edelman (1988).

1.1 Neurones using amino acids as transmitters
1.2 Neurone type: A-neurones, Aα, Aβ-fibres, myelinated, fast conduction velocity, encapsulated receptors, no evidence for transmitter release at peripheral terminals (in contrast to 2.4.2)
1.3 Subdivision according to neurochemical criteria
1.3.1 glutamate as transmitter
1.3.2 aspartate as transmitter
1.4 Subdivision according to functional criteria
1.4.1 nociception
1.4.2 proprioception, discriminative touch

2.1 Peptidergic neurones
2.2 Neurone type: B-neurones, A-delta and C-fibres, thinly or not myelinated, slow conduction velocity, free nerve endings. Considered here are those neurones that contain peptides that fulfill the following criteria: biosynthesis and presence in the neurone, release from terminals and known biological effects, i.e., substance P, NKA, NKB, CGRP, somatostatin, galanin; knowledge about many other peptides found in afferent fibres is less detailed at present.
2.3 Subdivision according to neurochemical criteria
2.3.1 capsaicin-sensitivity neurones: neurones containing one neuropeptide or more than one neuropeptide, NGF (nerve growth factor)-dependent, no re-uptake of released transmitters. The attribution of a specific function to the release of one neuropeptide is possible in many cases; it is, however, difficult if several transmitters are released jointly.
2.3.2 capsaicin-insensitive neurones: e.g., 4.4
2.4 Classification of neuronal function
2.4.1 Centripetal transmission of afferent signals
2.4.1.1 Signals reaching the level of consciousness ("polymodal")
2.4.1.1.1 nociception
2.4.1.1.2 heat sensation
2.4.1.1.3 mechanoreceptors
2.4.1.2 Reflexes
2.4.1.2.1 heat dissipation
2.4.1.2.2 circulatory reflexes
2.4.1.2.3 reflex release of adrenaline
2.4.1.2.4 reflex cholinergic secretion
2.4.1.2.5 micturition reflex
2.4.1.2.6 (motor reflexes in newborn rats)
2.4.1.3 Neuroendocrine regulation
2.4.1.3.1 ACTH release
2.4.1.3.2 decidua formation
2.4.1.3.3 vasopressin release (see also 4.4.1.1)
2.4.1.3.4 oxytocin release; (mediated also by 4.4.1.1 and by signals from sensory organs)
2.4.2 Functions mediated by peripheral release of peptides ("nocifensor system," "neurogenic inflammation," Chahl et al. 1984)
2.4.2.1 vasodilatation
2.4.2.2 plasma extravasation
2.4.2.3 histamine release from mast cells
2.4.2.4 miosis
2.4.2.5 bronchoconstriction
2.4.2.6 bronchial secretion
2.4.2.7 slow epsp's in inferior mesenteric ganglion

3.1 Purinergic neurones
3.2 Neurone type: B-neurones (?)
3.3 Subdivision according to neurochemical criteria
3.3.1 Capsaicin-sensitive neurones: adenosine or ATP as transmitter
3.4 Functional criteria: evidence for release has been found; function unknown

4.1 Unknown transmitters
4.2 Neurone type–B-neurones and unknown
4.3 Subdivision according to neurochemical criteria
4.3.1 Capsaicin-sensitive neurones: FRAP (sensory neuron specific ["fluoride-resistant"] acid phosphatase)-containing neurones (and possibly others)
4.3.2 Capsaicin-insensitive neurones: see 4.4.1
4.4 Subdivision according to functional criteria
4.4.1 centripetal transmission of afferent signals
4.4.1.1 portal vein osmoceptors mediating the release of vasopressin and oxytocin
4.4.1.2 cold-sensitive neurones
4.4.1.3 mechanoreceptors

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Can capsaicin be used to discriminate between subpopulations of B-afferents?

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I enjoyed reading Prechtl & Powley's (P & P's) contribution, which raises several interesting questions about the structure and function of B-afferents. Here I wish to focus the attention of the *BBS* readership on a topic that is not specifically addressed by the authors: the possibility that subpopulations of B-afferents might be distinguished by the use of capsaicin. Available data suggest that this could be the case, at least in rats.

(1) When administered in high doses (usually as a single dose of 50 mg/kg s.c. [subcutaneous]) capsaicin exerts a neurotoxic effect on B-afferents. Jancsó et al. (1977; 1985) found a marked quantitative difference in the extent of neurotoxic damage produced by capsaicin when the drug is administered to newborn or adult animals. In the former case, capsaicin produced a reduction of about 50% in dorsal root ganglion (DRG) neurons whereas in the latter case no more than 20% of the primary afferents showed signs of degeneration. Jancsó et al. (1985) therefore proposed that capsaicin desensitization in *adult* rats might be used to selectively inactivate a subpopulation of B-afferents. The complementary hypothesis is that a number of B-afferents that are capsaicin-sensitive at birth become, for some reason, capsaicin-resistant during postnatal development.

(2) Single unit recordings from the cutaneous nerves of adult rats indicate that capsaicin exerts a highly selective effect on *polymodal nociceptors* irrespective of whether their fibers have conduction velocities in the C- or the A-delta range (Szolcsányi et al. 1988; Szolcsányi 1989). After neonatal treatment, there was indiscriminate loss of functionally identified C-fibers from the skin but still restricted to primary afferents (Szolcsányi 1989). Szolcsányi proposed using the acronyms CSA (capsaicin-sensitive afferents in the *a*dult animal) and CSB (capsaicin-sensitive afferents in the new*b*orn animal) to distinguish between these populations. It should also be noted that after neonatal treatment at doses > 50 mg/kg s.c. a portion of A-type sensory neurons can also be destroyed by capsaicin (Lawson & Harper 1984; Szolcsányi 1989). [See also the accompanying commentary of Szolcsányi, this issue.]

(3) There is evidence that an excessive influx of calcium ions from extracellular space is involved in the neurotoxic action of capsaicin on primary afferents (Maggi & Meli 1988; Maggi et al. 1988; 1989a; Wood et al. 1988). Winter (1987) showed that cultured neurons from adult rat DRG can be distinguished as neurofilament (RT-97 antibody) positive (A-type) and neurofilament-negative (B-type). A method was developed to visualize capsaicin-sensitive neurons in culture directly by cobalt intake (which enters the cells via a cation-unselective, calcium-permeable channel opened by capsaicin). RT-97-positive neurons were capsaicin-insensitive. Among RT-97-negative neurons, only 50% of the elements were stained with cobalt on exposure to capsaicin. As a much larger fraction of RT-97-negative DRG neurons (84%) are killed by neonatal capsaicin treatment (Lawson & Harper 1984), a developmental change in the number of neurons sensitive to capsaicin was proposed (Winter 1987).

(4) Capsaicin-sensitive afferents have been reported to contain a variety of neuropeptides (see Holzer 1988, for review). Among these, a transmitter role seems likely for tachykinins (TKs) and calcitonin gene-related peptide (CGRP). These peptides are transported to both central and peripheral terminals of these primary sensory neurons, at which level their release determines sensory and "efferent" functions (Szolcsányi 1984; Maggi & Meli 1988). Available evidence indicates that after the administration of a single dose of 50 mg/kg s.c. of capsaicin to adult rats the TK and CGRP content of several organs, such as the urinary bladder (see below) is depleted (Abelli et al. 1988; Geppetti et al. 1988).

(5) Functional studies on the rat urinary bladder have shown that capsaicin-sensitive nerves play a fundamental role in the regulation of reflex micturition and other functions (see Maggi & Meli 1988, for review; Maggi et al. 1989b). The extent of reflex micturition impairment produced by capsaicin desensitization in adult rats is much lower than that produced in newborn rats. In the former group, bladder capacity is increased but micturition occurs normally at a high intensity of the stimulus to void. By contrast, in the latter group, reflex micturition is virtually abolished and marked bladder enlargement occurs. Capsaicin treatment (or desensitization) in adult rats inactivates a neurochemically identified population of bladder nerves that accounts for the whole content of TKs and CGRP of this organ. These bladder sensory nerves, which have been termed P1 nerves (where P stands for *P*opulation), play a modulatory or facilitative role on attainment of threshold for reflex micturition. In rats treated with capsaicin as adults, micturition can be activated by stimulating P2 nerves (capsaicin-resistant in adult rats but capsaicin-sensitive in newborn rats). The capsaicin-resistance of P2 nerves cannot be overcome by increasing the desensitizing treatment up to a dose of 350 mg/kg in adult animals (Maggi et al. 1989b).

In conclusion, I wish to add this brief note to P & P's review to underline the exciting possibility (which needs further experimental evaluation) that capsaicin might be used to define the anatomical, neurochemical, and functional properties of subpopulations of B-afferents. It is to be hoped that this will stimulate further work on qualitative/quantitative differences in the effects of capsaicin pretreatment in adult versus newborn rats (and other species as well). At this stage of our knowledge, it appears that neither type of capsaicin pretreatment is completely specific to B-afferents, as defined by P & P in their target article. When capsaicin is administered to adult rats, only a fraction of the B-afferents is affected. When capsaicin is administered to newborn rats, a larger fraction (about 84%) of B-afferents, but also some large light cells, are killed (Lawson & Harper 1984).

Somatic spikes of sensory neurons may provide a better sorting criterion than the autonomic/somatic subdivision

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It is clear from Figure 3 of the target article by Prechtl & Powley (P & P) that a number of anatomical and histological properties segregate coordinately between A- and B-neurons, which are suggested to function as somatic and autonomic afferents, respectively. Although one cannot quarrel with the fact that dorsal root ganglion (DRG) cells are heterogeneous, the question of their subdivision according to participation in somatic or autonomic reflexes is by no means clear. Indeed, (coccygeal) A-delta nociceptive neurons described originally by Burgess and Perl (1967), and classified here as autonomic afferents, terminate in two distinct regions of the spinal cord, lamina I and V (Light & Perl 1979) which, according to P & P's Figure 2b, are in the recipient zones of A- and B-neurons, respectively. Furthermore, many spinal neurons in laminae IV and V, defined operationally as wide dynamic range neurons (Mendell 1966), receive convergent functional (and possibly monosynaptic) inputs from afferents in both large light and small dark categories. This complexity of neuronal connectivity, both divergent and

convergent, complicates attempts to classify at a systems level. Similar difficulties have been encountered in classifying sensory neurons as "flexor reflex afferents" because these afferents are not homogeneous in their connections (reviewed in Baldissera et al. 1981).

These arguments are not meant to denigrate attempts at classification and indeed such activities often have heuristic value. The intrinsic appeal of classification can perhaps best be seen by the tendency for critics of one classification scheme to replace it by another! The purpose of this brief commentary is to present further evidence that afferent neurons can indeed be divided into two groups very much along the lines proposed in the target article; however, the defining factor may differ somewhat from the somatic/autonomic dichotomy suggested here.

A number of recent papers from this laboratory have revealed that the shape of the somatic spike of DRG neurons varies according to the receptor innervated in the periphery (Rose et al. 1986; Traub & Mendell 1988; Koerber et al. 1988; see also Strauss & Duda 1982)). The most robust of these findings is that cells with A-alpha and A-beta axons supplying low-threshold mechanoreceptors in skin or muscle exhibit narrow spikes in contrast to cells with unmyelinated fibers that have much broader spikes with a well-defined hump on their falling phase (presumably the result of a Ca^{++} component, see discussion in Koerber et al. 1988). Cells with A-delta axons innervating low-threshold mechanoreceptors (D-hairs) have narrow spikes, whereas those supplying high-threshold mechanoreceptors (nociceptors) have broad spikes with putative Ca^{++} components. Thermoreceptors have not yet been classified in this way. Thus, it appears that the A- and B-neurons described in the target article, and whose somatic spikes have been recorded, are distinguishable according to the shape (and ionic components) of these spikes.

Not all cells with A-beta axons can be identified as A-neurons (see Figure 3, target article) because there is a well-defined population of such neurons with broad spikes and high-threshold receptive fields (Koerber et al. 1988). C-fibers with a low-threshold adequate stimulus have broad spikes (Traub & Mendell 1988), so it is clear that the division between groups, however defined, is not according to the intensity of the adequate stimulus. Visceral afferents have not yet been classified according to spike shape except for chemoreceptors and baroreceptors in the nodose ganglion, which have broad and narrow spikes, respectively (Belmonte & Gallego 1983).

The common factor linking sensory neurons with broad spikes is not known at this time. It is tempting to suggest that they are all chemoreceptors, but present evidence does not permit nociceptors to be classified in this way (reviewed in Perl 1984) and it is difficult to imagine that low-threshold C-fiber mechanoreceptors function via a chemical intermediary. At present, it is difficult to assign properties to sensory receptors that covary with somatic spike configuration.

Developmental studies cited in the target article indicate that A-neurons are "born" (i.e., stop synthesizing DNA) before B-neurons. Spike configuration data provide a somewhat different perspective on this issue, at least in the rat, because all neurons exhibit broad spikes with humps in the neonate, even those destined to assume the properties of A-neurons (Fulton 1987). Narrowing of the spike occurs about two weeks after birth (Fulton 1987), which suggests that the cells born first mature to the greatest extent if one assumes that a narrow spike without a hump can be identified with the mature state (Spitzer 1979). The implication of spike shape heterogeneity is that the neurons in the adult DRG are nonuniform in their maturity. Neurons with broad spikes are less mature and the properties associated with immaturity (e.g., more Ca^{++} current) may account, for example, for their ability to sprout more profusely than cells with narrow spikes (see discussion in Koerber et al. 1988).

What is the biological significance of two populations of sensory ganglion cells? One class of explanation is related to cellular electrophysiology and consists of the prediction that the membrane differences of sensory neuron somata are indicative of corresponding differences in their synaptic terminals. It is known, for example, that the activation of nociceptors (but not low-threshold afferents innervated by large-diameter afferents) tends to cause a long-lasting central excitatory state originally described as the "windup" (Mendell & Wall 1965; Mendell 1966). Part of the explanation for this phenomenon may be related to the action of spinal NMDA-receptors (Dickenson & Sullivan 1987). However, if the synaptic terminals of these high-threshold afferents exhibit the same lack of inward rectification observed in their somata, one would anticipate central facilitation due to more prolonged terminal membrane hyperpolarization after a conditioning impulse. Such facilitation, inversely correlated with inward rectification in the soma, has been reported for sensory fiber projections (Koerber & Mendell 1988).

Another class of explanation (not exclusive of the first) for the existence of these two cell types is that the entry of Ca^{++} into somata generating broad spikes makes these cells more sensitive metabolically to levels of neuronal activity (through Ca^{++} regulation of second messengers) than cells with narrow spikes. Axons have not been reported to have Ca^{++} spikes (reviewed in Hille 1984), and so axonal function would not be under such control. This may be the biological significance of the pseudounipolar structure of sensory neurons. Axonal conduction is independent of activity, but impulses might regulate the function of cells with broad somatic spikes, e.g., their release of transmitter. This could represent an important feedback loop in the maintenance of homeostasis in agreement with P & P's proposed role for B-neurons.

In conclusion, the major point of the target article, namely, the existence of autonomic afferents, is not a subject of debate. However, the division of the afferent population into two groups based on their participation in somatic or autonomic activities is more questionable. It is argued here that a more appropriate criterion for subdividing sensory neurons is the nature of the somatic spike. The two schemes may give similar results, but the cellular physiology may provide better insight into function.

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Dichotomic classification of sensory neurons: Elegant but problematic

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The target article on afferent neuron classification by Prechtl & Powley (P & P) represents a refreshing attempt to both unify ideas on structure and function of primary afferents and minimize sources of error and misconception inherent to classical concepts. Its strength undoubtedly lies in the extension of the morphologically well-established A/B classification of primary sensory neuronal cell bodies to their peripheral and central terminals, combined with a more general functional dichotomy. Thus, confusions raised by the adherence to the somatic-visceral or sympathetic-parasympathetic dichotomies can be elegantly avoided. Such confusions have been caused mostly by implying too many functional suppositions in designators that were primarily gross morphological by definition. Some other "oddities" can be considered merely semantic, for example, the efferent "autonomic" and afferent "somatic" innervation of the dermis.

Avoiding the use of classical, somewhat overladen dichotomies, and describing afferents according to the organ they innervate or the pathway they travel (e.g., splanchnic, vagal, intercostal, and so forth, without the need to label them "visceral" or "somatic") has always been much less confusing and has provided a sound morphological basis for detailed functional studies. However, it is both intriguing and rewarding to formulate universal dichotomous classification that satisfies the needs of both anatomists and physiologists. The great heuristic value of such a system is obvious. And in fortunate cases such a classification may even come close to what can be considered a "natural" taxonomy. In this respect, P & P's concept is as important as the classical systems of Langley (1921) and Herrick (1903) have been.

To the examples of B-afferents included in P & P's Figure 4, one may add fine-calibre muscle afferents. There is ample evidence for their role in eliciting cardiopulmonary reflexes (see, for review, Mense 1986), and they may even specifically influence hypothalamic cell groups known to be involved in homeostatic regulation (Kannan et al. 1988). They are a good example of primary afferents that would benefit from the A/B classification, because the labels hitherto used for them (i.e., either "somatic" or "deep" – close to "visceral" – afferents) could not satisfactorily describe their ambiguous nature: Although they are distributed to muscles ("somatic" structures), their central termination pattern resembles "visceral" afferents more than "somatic" (skin) afferents (Craig & Mense 1983; Neuhuber et al. 1986).

Several points indicate that the proposed concept might produce new "oddities," however, as the classical ones did. For example, it is somewhat surprising that B-afferents thought to represent a primitive system which evolved early in phylogeny are born late in ontogeny. Furthermore, even with the understanding that every dichotomous classification has to be taken *cum grano salis*, it has to be asked whether the morphofunctional A/B dichotomy – i.e., B-afferents related to the autonomic nervous system (ANS) and homeostasis on the one hand and A-afferents related to skeletomotor systems and rapid reactions on the other hand – can be maintained without major modifications, or whether there is significant functional overlap between the two categories. Explicitly, are there significant populations of A-afferents that elicit ANS reflexes or are involved in homeostatic regulation? And are there relations of B-afferents to the skeletomotor system that are as close as those to the ANS?

Concerning the latter point, the only direct (i.e., monosynaptic) connection of B-afferents to the ANS that has apparent functional significance is that of thoracolumbar visceral afferents to prevertebral ganglionic neurons by means of collaterals (Matthews et al. 1987; for review, see Simmons 1985). To date, such collaterals have not been found in significant numbers in paravertebral or pelvic ganglia. Thus, they apply only to a minority of B-afferents. All the other connections between B-afferents and pre- or postganglionic autonomic neurons are polysynaptic. Monosynaptic contacts between B-afferents and spinal (for review, see de Groat 1986) or vagal (Ling et al. 1986; Neuhuber & Sandoz 1986; Rinaman et al. 1989) preganglionic neurons as demonstrated morphologically are probably of little functional significance (de Groat et al. 1981; Nosaka 1986). Hence, the majority of B-afferent-to-ANS connections do not differ from connections to the skeletomotor system, which is reflexively activated via polysynaptic pathways by B-afferents from skin, muscles, and viscera (Mense 1986; Ness & Gebhart 1988) as part of the "network of defense" (Lembeck 1987).

As to the first point, there do exist afferent fibers in significant numbers that belong to the Aβ/II class connected (most probably, though this has not been demonstrated histologically) to A-type cell bodies, and that elicit autonomic reactions and contribute to homeostasis. Let me first consider Aβ splanchnic afferents. Although they are considered "exceptional" by P & P, they amount to several hundreds in the cat (Kuo et al. 1982) and, upon stimulation, produce mass reflex discharges in white rami (Sato & Schmidt 1973). Unfortunately, nothing is known about the physiological significance of this autonomic response. More significant are reports of strong reflex responses in cutaneous vasomotor and renal sympathetic fibers upon stimulation of cutaneous II afferents (for references, see Sato & Schmidt 1973). Third, the numerous vagal slowly adapting and some of the rapidly adapting tracheobronchial stretch receptors with conduction velocities in the Aβ range (Sant'Ambrogio 1982) have to be taken into account. These neurons surely contribute to homeostasis. One may argue that the latter case exemplifies the close relation of A-afferents to the skeletomotor system, because the influence on ventilation exerted by these stretch receptors is mediated, at the efferent side, by skeletal muscles, that is, the diaphragm and intercostal muscles. Then, however, one must admit that homeostatic functions are also subserved by the skeletomotor system.

Taken together, these examples do not of course invalidate Prechtl & Powley's proposal as it is shaped for a majority of spinal B-afferents (see their Figure 4). However, they do call into question the general applicability of such morphofunctional dichotomies. And they indicate that the "weld" between skeletomotor and autonomic parts of vertebrates is much more perfect than suggested, thus rendering dichotomous classification a difficult task.

B-afferents: An important afferent input to the autonomic reflexes

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This target article gives us important and valuable information on the roles played by A-neurons and B-neurons in the dorsal root ganglia. Prechtl & Powley (P & P) indicate that the "large light" A-neuron class is known to consist predominantly of proprioceptive and mechanoreceptive afferents and the "small dark" B-neuron class mostly of thermoceptive and nociceptive afferents. P & P outline an association between autonomic and B-neurons based on ontogeny, cell phenotype, and functional relations, grouping them together as part of a common reflex system involved in homeostasis.

There are some problems in terminology, however. P & P write that the B-neurons in the dorsal root ganglia receive A-delta afferents (thin myelinated ones) and C-afferents (unmyelinated ones) from the periphery, and as shown in their Figure 4, there are several different B-afferents (visceral, viscerocutaneous, and cutaneous) that send sensory signals to B-neurons in the spinal ganglia.

In addition, the sympathetic (preganglionic) B-neurons (Nishi et al. 1965) with thin myelinated efferent B-fibers in the spinal cord receive reflex inputs from afferent B-neurons in the spinal ganglion. The sympathetic postganglionic neurons and postganglionic nonmyelinated fibers are sometimes called C-neurons and C-fibers. This pathway plays an important role in autonomic reflexes and homeostasis. To avoid a confusion in terminology, it might be desirable to use the expression "d.r.B" for afferent B-neurons in the spinal ganglion and "s.B" for sympathetic preganglionic neurons because s.C and d.r.C have already been used in textbooks of physiology (Fulton 1955).

Neuromodulatory activity of peripherally administered substance P

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Prechtl and Powley (P & P) summarize many results that support the existence of afferent neurons in the autonomic nervous system. Investigations of substance *P* (SP) carried out in our group since the beginning of the seventies conform with the thesis of an afferent feedback control of vegetative functions.

Oehme et al. (1980) and Hecht et al. (1980) discovered an antistress activity of SP. In rats, for example, peripherally administered SP (250 μg/kg intraperitoneally injected on four consecutive days) inhibits the blood pressure increase induced by immobilization (Roske et al. 1983). It is interesting that the effect of SP actually lasts longer than pharmacokinetic data suggest. When SP is administered once a day for four days the effect on blood pressure lasts longer than 24 hours.

Analogue examples are known from other peptides. The tripeptide Pro-Leu-Gly-NH_2 (MIF-1, MSH release-inhibiting factor) given once a day (1 mg/kg) alters the development of opiate tolerance (delayed tolerance to the analgesic action of morphine; Kastin et al. 1979). The MIF-1 derivative cyclo (Leu-Gly) exerts the same activity even after intragastric administration (Bhargava 1988). All these findings suggest that several peptides and opiates administered outside the central nervous system (CNS) interact with regulatory processes in the CNS by influencing peripheral sites and by transmitting information via afferent neurones. On the other hand, there is feedback regulation of peripheral processes. Recent findings of Höllt et al. (1989) show that in rats peripherally administered morphine induces vice versa via a central mechanism an expression of the enkephalin gene in adrenals.

The hypothesis that capsaicin-sensitive fibers constitute a "neurogenic alarm system" or a "network of defense" (Lembeck 1987) agrees with our findings. In our opinion, SP especially plays an integrative role in stress defense. Typically SP influences deviations from the normal state, it normalizes disturbed physiological processes. We found that SP induces very different effects in analgesic tests. When using the current intensity threshold for evoking vocalization by stimulation of the mouse tail, SP increased the threshold in several animals, decreased it in others, and evoked only minimal changes in a third subgroup. The original state of the animals is decisive: SP acted as an analgesic in mice with a low nociceptive threshold. Otherwise, in animals with a relatively high nociceptive threshold, SP increased pain sensitivity. Animals with a moderate threshold did not react to SP (Oehme et al. 1980a).

Furthermore, peripherally administered SP can have a therapeutic as well as a prophylactic influence on even complex functions of the CNS, when disturbed by stressors, for example, disturbed learning and memory (Hecht et al. 1982).

The sites of action involved in the stress-protective activity of SP are not yet well known. We consider the adrenals to be among the most important targets. The adrenals are supplied by SP-containing fibers. Furthermore, we found SP-containing cells in the adrenal medulla (Görne et al. 1984).

Under stressful immobilization the SP content of the adrenals was strongly decreased. The low level of SP is the final state that follows increased release during stress (Roske et al. 1983). In this connection one can frame the hypothesis that substance *P* is involved in information transmission to the CNS and that it simultaneously controls vegetative processes. According to our investigations, SP limits the release of catecholamines from adrenals, for example. In adrenal slices in vitro SP preferentially inhibits electrically evoked acetylcholine release which results in an indirectly diminished release of catecholamines. The direct SP effect on catecholamine release is less pronounced (Nieber & Oehme 1987).

To summarize many new, pathophysiologically important aspects can be expected in the future from investigating the interaction of peptides with classical transmitter systems. Prechtl & Powley's target article presents interesting facts in this field.

Capsaicin-sensitivity and the sensory vagus: Do these exceptions prove or disprove the B-neuron rule for autonomic afferents?

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The addition of an anatomically defined sensory component to the autonomic system will be intellectually parsimonious only if the rules that define it admit few exceptions. In this regard, we would like to comment on the validity of using capsaicin-sensitivity to identify B-neurons. We would also like to discuss the perceived difficulty with which the B-neuron concept deals with the autonomic afferents of the vagus nerve.

Sensitivity to capsaicin-induced destruction is not a trait unique to B-neurons. One of us (Ritter & Dinh 1988) has demonstrated that capsaicin causes degeneration of neural elements in areas of the central nervous system not known to contain primary sensory neuron somata or to receive primary sensory terminals. These findings indicate that some brain neurons share characteristics previously thought to be unique to small unmyelinated sensory neurons. In addition, recent evidence indicates that some neurons of the enteric nervous system are sensitive to capsaicin (see Kirchgessner & Gershon 1988). Although these neurons might be sensory in function, their location is not typical of the B-neurons proposed as autonomic afferents. The fact that capsaicin-sensitivity is not unique to B-neurons does not damage Prechtl & Powley's (P & P's) thesis that autonomic sensory neurons are capsaicin-sensitive. It does indicate that capsaicin-sensitivity may not be used as a litmus for the inclusion of a neuron population in the autonomic afferent category. In this regard it is also interesting that P & P point out the presence in the dorsal root ganglia of non-capsaicin-sensitive mechanoreceptive B-neurons. According to P & P, these mechanoreceptive B-neurons may not be involved in autonomic function. However, both the gastrointestinal tract (gastric mechanoreceptors) and the vasculature (baroreceptor afferents) are innervated by non-capsaicin-sensitive stretch-receptive afferents (see, for example, R. C. Ritter et al. 1989). Because these visceral sensory neurons are clearly involved in autonomic reflexes, it would be hard to use either lack of capsaicin-sensitivity or mechanoreceptivity as exclusionary criteria for autonomic afferents.

P & P propose that the B-neurons may be *the* autonomic afferents. The criteria used to identify autonomic afferents anatomically as well as functionally, however, would exclude vagal afferents and possibly other nonspinal sensory fibers that clearly participate in autonomic function. As P & P point out, the nodose ganglion is of placodal rather than neural crest origin. Thus it may differ ontogenetically from B-neurons. In addition, unlike the B-neurons and sympathetic efferents, the vagal sensory neurons do not seem to depend on nerve growth factor (see, for example, Dimberg et al. 1987 and MacLean et al. 1988). Most, but not all, vagal afferents are capsaicin-sensitive, but only relatively small proportions of them contain any of the peptides associated with B-afferents of the dorsal root ganglia (e.g., see Dockray & Sharkey 1986).

Finally, P & P suggest that B-neurons generally provide an afferent limb for "rejective" or "defensive" autonomic reflexes. Such a rejective or defensive description does not generalize among vagal afferents, however. Many of the reflexes for which vagal afferents serve as the sensory limb are not "defensive" in the narrow sense associated with sympathetic function. They would be better described as "accommodative" or "sustaining." Consider, for example, receptive relaxation of the stomach.

Hence, although the autonomic function of the vagus is indisputable, we wonder whether the vagal sensory component can be made to fit the B-afferent categorization of autonomic afferents proposed by Prechtl & Powley. In as much as autonomic efferents can be separated into sympathetic and parasympathetic groups, with differing anatomic, ontogenetic, and functional identities, it may be that autonomic afferents also subdivide into several classes, with the B-neurons accounting for only one such class.

Capsaicin-sensitive chemoceptive B-afferents: A neural system with dual sensory-efferent function

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I agree with Prechtl & Powley (P & P) that the role of B-afferents in autonomic regulation needs reevaluation (Szolcsányi 1982; 1984; 1988). There are crucial differences in the principles we advocate, however. I think Langley (1921) was right not to form a class of afferents dedicated to initiating autonomic, homeostatic reflexes.

(1) Natural stimulation of a single well-defined group of sensory receptors often evokes a combination of somatic and autonomic reflexes and sensations. For example, an acoustic stimulus (a chick) elicits both a somatic reaction (startle) and autonomic reflexes (changes in heart rate and so forth). Autonomic reflexes are labeled by indicating both the input and output sides of the reflex arc, as with somatosympathetic reflexes, or, more precisely, musculocardiac chemoreflexes (e.g. Sato & Schmidt 1987). In a multineural reflex arrangement, designating the input element by an output function allows the possibility of reductionism and inconsistency.

(2) Natural or electric excitation of Group III and Group IV (A-delta and C-) afferents results in various autonomic reflexes. The same holds true, however, for some somatic (Sato & Schmidt 1987) or visceral Group II afferents, e.g., the aortic baroreceptors (Paintal 1972). Thus, A-type sensory neurons cannot be excluded in the initiation of homeostatic autonomic reflexes. On the other hand, the slowly conducting group comprises low-threshold mechanoreceptive units (cutaneous C-mechanoreceptor, D-hair receptor) that can be activated by gentle stimulation, as can various A-beta cutaneous mechanoreceptors (Burgess & Perl 1973). B-type sensory neurons are functionally heterogenous (Sugiura et al. 1988); consequently, their role in autonomic regulation differs significantly.

(3) We showed 20 years ago that capsaicin has a selective effect on B-type primary afferent neurons (Joó et al. 1969). Subsequent single unit studies have shown that in adult animals (but not after neonatal treatment of the rat) C-polymodal nociceptors, A-delta mechanoheat-sensitive nociceptors, and warmth receptors, but not other cutaneous units, are stimulated and desensitized by the drug (Szolcsányi 1984; 1987; Szolcsányi et al. 1988a). More than half of the cutaneous afferent C-fiber population consists of polymodal nociceptor units and belongs to the B_2 subtype of dorsal root ganglion (DRG) neurons (Sugiura et al. 1988). Because capsaicin has a selective effect also among interoceptors, I have proposed a pharmacological classification for primary afferent neurons and coined the term "capsaicin-sensitive afferents" (Szolcsányi 1982). Enteric, sympathetic or parasympathetic efferent nerves and neurotransmission processes are not influenced by the agent. The term has therefore been accepted and the drug has become as useful a tool in revealing afferent neural mechanisms as atropine is now, or as the ergot alkaloids were many decades ago when the classification of the autonomic nervous system was done (Holzer 1988; Maggi & Meli 1988; Szolcsányi 1984).

(4) Capsaicin-sensitive, slowly conducting afferents have two cardinal features:

(a) Their sense organs are chemoreceptors in that they are responsive to different chemical agents (e.g., to bradykinin) in concentrations that do not elicit discharges in other types of receptors (Szolcsányi 1984; 1987).

(b) Orthodromic or antidromic excitation of these nerve endings elicits discharge of mediators (Substance *P*, CGRP, and so forth) from them. The results are local responses of effector organs (vasodilatation, inflammation, increased cardiac function, and various visceromotor effects in the gastrointestinal, urinary, and respiratory tract, and so forth; cf. Holzer 1988; Maggi & Meli 1988; Szolcsányi 1984). Because neurogenic tissue changes (plasma extravasation and smooth muscle responses of various isolated preparations) to capsaicin-type agents are not inhibited by tetrodotoxin, it has been suggested that polymodal cutaneous nociceptors and other capsaicin-sensitive nerve terminals serve as sensory effectors (Holzer 1988; Maggi & Meli 1988; Szolcsányi 1982; 1984; 1988). In other words, the same nerve endings of these B-afferents are the sites for the release of mediators that subserve the triggering of sensory impulses toward the central nervous system. This feature enables the capsaicin-sensitive sense organs to evoke local tissue reactions without the intervention of an axon reflex and to mediate effector responses at both terminals of an axon reflex arrangement (e.g., flare response in the human skin).

(5) Experimental evidence obtained in many laboratories (for references, see Holzer 1988; Lembeck 1987; Maggi & Meli 1988; Szolcsányi 1984) suggests that in various organs the dual role of capsaicin-sensitive B-afferents forms an ultrashort protective neuroregulatory organization for modifying autonomic functions. The following data and considerations indicate, however, that this neural mechanism is not restricted to triggering "nocifensor" responses. A single antidromic electric shock is sufficient to enhance cutaneous microcirculation, i.e., to elicit antidromic vasodilatation. This "autonomic" effect is mediated by polymodal nociceptors and is absent if either the nerve or the whole animal is pretreated with capsaicin several days before the experiment. On the other hand, few spikes or very low frequency (e.g., 0.1 Hz) discharges of polymodal nociceptive units are unable to provoke nocifensive reflexes in animals or to elicit pain in humans (Szolcsányi 1987; 1988). Furthermore, perineural pretreatment of the sciatic nerve of the rat results in a decrease in cutaneous microcirculation of the corresponding hindpaw (Sann et al. 1988). It has been concluded that at threshold stimulation, capsaicin-sensitive B-afferents participate in the regulation of cutaneous microcirculation (their physiological role), whereas suprathreshold stimulation is needed to provoke nocifensive reflexes, pain sensation, and local neurogenic inflammation (pathophysiological role; Szolcsányi 1988; Szolcsányi et al. 1988b).

The powerful sensory-efferent function of a substantial portion of B-afferents in a large range of organs justifies the subdivision of primary afferent neurons on a functional basis. Myelinated or unmyelinated low-threshold mechanoreceptive afferents do not have similar local effector roles in autonomic regulation.

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Against rigid classification

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I find this attempt to subdivide afferents into two rigid classes to be jumbled and premature, based on a poor understanding of the old literature and a highly selective sample from modern literature. The confusion begins on the second page even in Prechtl & Powley's (P & P's) use of letters. A and B refer on occasion to morphological characteristics of dorsal root ganglion cells; on randomly interwoven other occasions, the same letters refer to Erlanger and Gasser's use of A, B, and C to refer to groups of fibres with different conduction velocities. By the last page we are subjected to the full nineteenth-century claptrap used to specify classes. The B- cells are "primitive," capable of only "simple" functions. These words are borrowed without embarrassment from the old classifiers of species and races. Then we are treated to yet another version of "ontogeny recapitulates phylogeny." Inside all of us is a hidden, simple, primitive nervous system concerned only with housework, a "dog beneath the skin." Furthermore, we have evolved from a pure B-animal that was nothing but a sedentary length of intestine. We escaped from this pitiful state by overlaying the B-system with a new fast complex A-system. Poor Romer, to whom this is attributed, must be groaning in his enforced sedentary state because his major point was that these marvelous coelenterates alternated between highly mobile and sedentary phases!

The major problem with P & P's speculation is that they rely inordinately on the significance of morphology and emphasise little of what is known about function and, more important, what is *not* known about function. The role of afferent fibres in the development of the periphery and of central connections in the embryo is not mentioned. Therefore, it is not surprising that their role in the modification of central nervous connectivity in the adult is missed. The interaction between target tissue, sensory axon chemistry, and central function in embryos, neonates, and adults is missing. It is easy to label fibres as simple if you still believe that their only function is to transmit nerve impulses that excite central cells by way of single transmitters such as substance P. In order to maintain this simplicity, it is necessary to ignore the past 20 years of work on cotransmitters, on fast and slow central changes, on the transport of chemicals both to and from the periphery, and on interactions between A- and B-cells or A- and C-fibres.

Instead of rushing to impose yet another rigid separate classification on the nervous system, I hope we will retain the caution of Langley until we know more of function. That does not mean that particular parts of the nervous system do not have particular functions at particular times. The nervous system copes with challenges from tissue within the body and from sources outside the body. It integrates these challenges from within and without to produce single response patterns. We are not class-A complex animals dragging around a class-B automatic fire alarm and sewage system.

B-neurons mediating homeostasis and behavior?

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Prechtl & Powley (P & P) have presented a solid case for the existence of a class of neurons dedicated to autonomic function. It should come as no surprise that the autonomic nervous system requires input from the "periphery" to coordinate and maximize the response efficiency of its effectors. Thus, it can be suggested that the existence of an afferent limb of the autonomic nervous system makes good functional sense. The accumulating body of anatomical evidence presented in P & P's target article lays a broad framework for enthusiastic debate and future experiments to investigate whether or not their hypothesis is substantiated both anatomically and functionally.

Despite the comprehensive survey of anatomical data in their review, further consideration of the functional significance of autonomic afferents is necessary. Indeed, the defense of homeostasis can be regarded as a crucial function for the autonomic nervous system. In addition, a neurogenic alarm system may be part of an autonomic mechanism to defend a homeostatic "set point." The response to deviations from the set point, however, should not be assumed to be independent of the animal's behavior because the animal's behavioral state sets the parameters for the response of the visceral effectors. Conversely, the functional limits of the visceral effectors may impose behavioral constraints on the animal. Thus, the autonomic nervous system may be charged with the duty of monitoring the internal milieu via a system of afferents and of initiating, via its efferent neurons, physiological changes that serve the animal's needs. B-neurons may participate in these reflexes but may also be involved in the control of behaviors that are consistent with the physiological changes. In this manner, afferent neurons that are "dedicated" to autonomic function may have higher-order effects that integrate behavior with autonomic mechanisms.

The neurotoxin capsaicin has emerged as a useful tool for the study of small unmyelinated afferent neurons and their role in autonomic function and behavior. For example, capsaicin-sensitive vagal afferent neurons have been implicated as mediators of reflex loops controlling gastric emptying, motility (Raybould & Tache 1988), and adrenaline secretion (Donnerer 1988; Amann & Lembeck 1986). Intestinal hyperemia induced by intraluminal infusion of oleate (a long-chain fatty acid) appears to be another autonomic reflex that is sensitive to capsaicin treatment, but the anatomical location of capsaicin-sensitive neurons in this case is not clear (Rozsa et al. 1986; Rozsa & Jacobson 1989). Thus, the anatomical substrates for some autonomic reflexes appear to include B-afferents. In some cases, however, capsaicin treatment does not abolish these reflexes altogether. This suggests that other neurons besides B-neurons participate in autonomic reflexes. The question is then raised as to whether a class of A-neurons is "dedicated" to autonomic function, as well.

The participation of capsaicin-sensitive vagal afferent neurons in autonomic reflexes is particularly interesting because a similar class of vagal neurons has been proposed to participate in the control of food intake. Yox and Ritter (1988) have demonstrated that capsaicin treatment attenuates or abolishes the suppression of feeding induced by intraintestinal infusions of oleate, maltose (a disaccharide), or l-phenylalanine. Moreover, it appears that afferent neurons in the vagus nerve mediate maltose- or oleate-induced suppression of food intake (Yox et al. 1988). Electrophysiological data suggest that afferent C-fibers respond specifically to either glucose (Mei 1978), amino acids (Jeanningros 1982), or fatty acids (Melone 1986) in the intestinal lumen. Most of these have been studied in the vagus nerve, but splanchnic chemoreceptive neurons may exist as well (Perrin et al. 1981). Furthermore, in rats, capsaicin-sensitive vagal afferents may also participate in the initiation of a behavioral sequence that occurs postprandially (Ritter et al. 1986). This suggests that autonomic reflexes and behavior may depend on substrates that are pharmacologically and anatomically indistinguishable. It is speculative as to whether or not B-afferents represent a common ascending pathway toward different functional ends, but the data indicate that homeostatic and behavioral mechanisms are highly integrated and may be extremely difficult to separate anatomically.

What about B-afferents and homeostasis from a systemic point of view?

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Until recently the prevailing view has been Langley's that the autonomic nervous system is exclusively efferent, innervating smooth muscles and glands and providing trophic innervation to skeletal muscles. According to this view, the autonomic nervous system consisted of both central and peripheral parts. At the same time there was also a notion that it consisted of exclusively peripheral neural structures. Neither conclusion seems correct today.

As long ago as 1944 Chernigovski wrote that few were the autonomic physiologists who could resist the temptation to pronounce on the existence of sympathetic afferent fibers, fewer still those who really tried to obtain experimental data on their presence or absence, and none who took on the hard but honourable task of studying this problem systematically. Yet many basic problems concerning the transmission of interoceptive stimuli could be seen in quite a new light if the existence of sympathetic afferent fibers could be demonstrated.

After much time and careful study one can now be sure of the existence of afferent nerves in the autonomic nervous system. It is a pity, however, that the references cited in Prechtl and Powley's [P & P's] nice survey do not include some of the papers of leading Soviet scientists (Bulygin & Soltanov 1973; Bulygin & Kaljunov 1974; Chernigovski 1944; 1960; Nozdrachev 1983; Zavarzin 1950). This suggests that their methodological approaches and interesting experimental data may still be unknown to English-speaking scientists.

P & P's target article touches on one of the interesting aspects of the morphofunctional properties of afferents in the autonomic nervous system. The authors present convincing histological evidence of the involvement of B-afferents in autonomic function. P & P's analysis of ontogeny, cell phenotypes, neurotransmitters and neuromodulators of peptide origin, and the functional relations of B-afferents suggest that B-afferents may participate directly in the common reflex system involved in homeostasis. However, despite the comprehensive morphological analysis with contemporary neurochemical methods, P & P's bridge across the gap between structural properties of B-afferents and their involvement in homeostasis is very unsteady.

The main reason for these problems, in my view, is that P & P emphasize direct reflexive connections of B-neurons and the involvement of B-afferents in maintaining some classic reflex functions. Good examples are P & P's explanation of the role of B-afferents in nociception and of the role of capsaicin-sensitive B-afferents; according to Lembeck (1987), these constitute a "neurogenic alarm system" or a "network of defense" (sect. 4.1, para. 6).

These arguments seem to me to involve some of the tunnel vision typical of many contemporary morphologists in their attempts to explain the physiological mechanisms of homeostasis from classic reflex theory. In his remarkable and timeless treatise on the integrative action of the nervous system, Sherrington (1906) argued that pure or simple reflexes do not exist in normally functioning animals "because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts and it is a system certainly never absolutely in rest."

Thus, an oversimplified view of the physiological mechanisms of homeostasis creates additional problems for P & P's explanation of the role of B-afferents. Although a detailed discussion of contemporary general system theories is not possible here, I should like to stress that the hierarchical levels of the physiological mechanisms of homeostasis, including goal-directed behaviors, cannot be successfully interpreted through classic reflex theory alone.

Various systemic approaches to physiological mechanisms of homeostasis, including Anokhin's system theory of organismic function (1968), which is being successfully developed in leading scientific research institutes in the USSR, make it possible to overcome many of the limitations of classic reflex theory. They also raise a lot of questions about the goal-directed behavior required to maintain homeostasis because "no animal is a passive respondent to environmental commands" (Marler & Hamilton 1966).

What about the role of B-afferents in feedback mechanisms needed for goal-directed responding and for maintaining homeostasis. How to explain the role of B-afferents in the regulatory trophic effects of the autonomic nervous system, i.e., maintaining optimal metabolism in the efferent organs, including skeletal muscles, that are involved in various behavior patterns. P & P's target article provides no explicit answers to these and other questions.

P & P's comprehensive survey of the latest neurohistological and neurochemical data leaves open the main question of whether B-afferents can be considered to be a "fundamental division of nervous system mediating homeostasis." This question probably represents one of the more attractive features of Prechtl & Powley's overview because it stimulates a broad diversity of scientists – neurohistologists, physiologists, neurologists, and representatives of the behavioral sciences – to make new efforts to solve the basic problem of the role of afferent autonomic nerves.

Authors' Response

Ontogeny, form, function, and prediction

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The commentaries have suggested new interpretations and have brought to light issues and ambiguities that would otherwise have escaped our attention. Most of the commentaries can be sorted into a few well delimited groups but we will resist this temptation to classify. (Yes, we jest!) Our target article critiqued the peripheral nervous system (PNS) classifications of Herrick (1903; 1927) and Langley (1903; 1921) and used them as a springboard to propose an extension of the A-B classification of dorsal root ganglion neurons. Although some commentators accepted Langley's provisional decision not to delineate a group of afferents particularly associated with the autonomic nervous system (ANS), none appeared committed to a systematic defense of the traditional classification. Rather, about half of the commentators were receptive to an alternative classification, whereas the remainder, for various reasons, asserted that a new systematics would be premature, impractical, and/or equally problematic. These points are addressed in section 1. Of the former group, some had misgivings about the boundaries or criteria we proposed, and a few others had developed alternative supplementary classifications of their own. We discuss these issues in section 2.

Three other broad sets of issues were raised repeatedly in the commentaries. A number of commentators took issue with our having limited our argument for association

between afferent populations and the autonomic nervous system to the dorsal root ganglion afferents. In this set, different reviewers argued that other populations of "visceral afferents" or "autonomic afferents," including particularly vagal nodosal afferents, should be included in any classification. These ideas and related issues are addressed in section 2. Our second hypothesis, "The ANS is the motor system most closely related to the B-neuron division," received perhaps the most opposition, particularly on the dimension of reflex function. This issue is examined in section 3. Finally, a few authors took issue with our speculation on evolutionary significance. This point is discussed in section 4.

Before considering the ideas that commentators have raised, though, we would offer the reminder that a review of the points of contention should not obscure the many areas in which our target article and the commentaries agree or in which no controversy has surfaced. Two cases deserve special emphasis. First, we had stressed the importance of the ontogenetic commonalities between the B-neurons and autonomic motor neurons. As we indicated, this ontogenetic criterion is the signal trait of the polythetic classification we proposed. None of our commentators challenged, or even reinterpreted, the supporting data or the commonalities we listed.

The second salient set of observations the commentators did not contest was that disturbances co-occur in B-afferent functions and autonomic functions in several clinical syndromes. As the target article indicated, these correlations point to commonalities between B-afferents and autonomic effectors; they also illustrate the heuristic value of our proposal and suggest practical tests of the idea.

The following sections, however, focus on the issues and controversies raised in the commentaries, rather than on the substantial common ground.

1. Biological classification: Real and ideal, or do the exceptions obviate the plan?

> It was a source of considerable distress, from the earliest period of classification on, that certain individuals or species were found which lacked one or the other character "typical" (that is, essential) for the taxon. – Mayr (1982, p. 189)

All of us would prefer a discrete and symmetrical classification reminiscent of chemistry's periodic table, but experience has established that biological sets (i.e., populations) are not amenable to such an ordering. **Cervero** and **Ritter & Ritter** make trenchant points in cautioning against a classification with many exceptions, but we should expect some and tolerate them in proportion to the generalizing power of the classification. If the classification permits generalizations about many different neuron populations of different animals, then some exceptions are a small price to pay: Consider the value of the class mammalia despite the odd members it incorporates such as the duck-billed platypus. Many of our most appreciated and unquestioned classifications would turn up exceptions if we were to try to justify them formally with a list of delimiting traits.

In this light, it is useful to reconsider the ANS, i.e., the fundamental concept to which we propose an addendum. The concept of the ANS is littered with exceptions to each of its defining traits. Violating the cardinal autonomic rule or criterion closest to a defining trait, some sympathetic postganglionics are cholinergic. In addition, some postganglionics are neither cholinergic nor adrenergic. Some postganglionics are specialized effectors or endocrine organs rather than final common paths synapsing on effectors. Some (modified) postganglionics are found in the brain. White rami are not exclusively white (or myelinated). Gray rami are not entirely gray (or unmyelinated). Ganglion cells are not always in ganglia; rather, they, along with glomus tissue, are often found in widely dispersed islands within the nerves. And such a list of heterodoxies is not exhaustive.

It is this backdrop of ANS heterogeneity and complexity we had in mind when we were proposing that the B-afferents were more closely allied with the ANS. We did not assume that any class associated with the ANS would be more monolithic and exception-free than the ANS itself. It is also because of this complexity that we stressed that our idea of classification was polythetic rather than monothetic (see footnote 4 in target article). Given that ANS exceptions are legion and widely accepted, we assumed that our commentators would start from a similar set of expectations concerning classification. This may have been a misjudgment on our part. Perhaps we should have stressed the heterogeneity of the classical elements of the ANS. Certainly none of the commentators argued that the manifold exceptions that complicate our concepts of the ANS were grounds for throwing out the concepts in their entirety. By the same token, the several exceptions and qualifications to the B-afferent category (see below for a discussion of the separate points) do not impeach the construct before the fact. One might argue, only partially tongue in cheek, that any trait that did obtain in the ANS without exception or variation should be suspect as a discriminative marker.

Some applications of the somatic-visceral labels are perhaps free of exceptions, but they tell us little about the designated neurons except for their general innervation territory. Because the somatic-visceral distinction is useful for comparing different nerves it might be considered a special purpose classification. We have promoted the A-B grouping as what taxonomists call a "natural" or "predictive" classification (see Stace 1980). Such classifications serve as orderly systems for storing and retrieving a variety of facts and making inductive generalizations. Thus, although B-neurons are currently grouped because they share certain traits, we suspect that they will later be found to share other traits as well. For the most part, the long-recognized groupings of orders and families of organisms based on morphology have predicted the recent results of DNA-DNA hybridization studies (see Sibley et al. 1988).

The B-neuron hypothesis is thus both promising and disappointing. It is both because it is not (as **Cervero** suggests) a grand classification scheme. Instead, it deals with a circumscribed group of ganglia, acknowledges the probability of other smaller but taxonomically distinct groupings within these ganglia, and, more important, it is constructed with the principles of biological classification in mind. The approach we have taken in comparing the different neurons is similar to that of Pearse (1969) in the grouping of APUD (amine precursor uptake and decarboxylation) cells, or that of Fujita & Kobayashi (1979) with

their "paraneuron" concept. Recently, Rowell (1989) proposed the creation of a new field, the "taxonomy of invertebrate neurons," also advocating the application of the procedures of organism taxonomy. Admittedly, our analogizing neuron classification with taxonomy is ambitious because we have neither full skeletons to work with nor established ideas about what would constitute a neuronal species, but it is a starting point for such a systematics.

1.1. To classify or not to classify. Some commentators have questioned the usefulness of further classification. We would argue that it is, in any case, unavoidable. Classification is so fundamental to science and cognition that it usually goes unnoticed. Many workers claim they use the terms "visceral afferents," "somatic afferents," and so forth, in an atheoretical, noncommittal, and nonclassificatory way. Although this may avoid some immediate argument or discussion, probably no philosopher of science, epistomologist, or taxonomist would accept that you can classify without classifying! The more practical question might be: Should we explicitly aim for a predictive classification or content ourselves with a few traditional schemes and a multitude of special purpose classifications? Specialists may be satisfied with one or more of special purpose classifications that tightly organize observations about a particular trait (e.g., sensitivity to anoxia). But the student, the textbook author, and the teacher have difficulty in sorting all the seemingly disparate facts contributed by the different disciplines. To put this issue in a fuller light, it is important to remember that the commentaries have come from the specialists and experts in the field who are close enough to the problem to allow for all the nuances, subtleties, and exceptions. The much larger constituency of nonspecialist end-users who need a more global systematics to help discern the forest from the trees is not represented in the commentaries.

We disagree with **Wall** that our classification efforts are premature. The classification systems of organisms have emerged over the past two centuries by a process of gradual improvement with the discovery and incorporation of more and more taxonomically valuable traits (Stace 1980). We cannot wait for all the relevant facts to be gathered before attempting a classification. Indeed, until such attempts are made we cannot know which facts will be relevant.

1.2. Nomenclature. The issue of conflicting nomenclatures is raised by **Grundy, Niijima,** and **Wall.** We too regret the unfortunate confusion that can result when scientists name differing types as A, B, and C. Imagine, for example, that **B**-neurons with A-delta fibers release neurokinin-B near pancreatic A-cells and elicit reflexes involving the B-fibers of preganglionic sympathetic neurons. Troubles could multiply in the case of frogs where postganglionic neurons are also divided into B- and C-classes.

An unambiguous new vocabulary for the peripheral nervous system is undoubtedly desirable, but is more than we have undertaken to provide. In the target article we consistently used the A-B-C terminology of Gasser and Erlanger (1929; Table 1 of target article), as originally intended, to designate fibers of certain conduction velocities; moreover in discussing A-fibers we added the Greek letter qualifiers (i.e., beta, delta). After the work of Gallego and Eyzaguirre (1978) some authors use the term "C-cells" to refer to all nodose ganglion neurons that have slowly conducting axons (<3 m/sec) and "A-cells" for the remaining nodose ganglion neurons. This potential source of confusion with the root-ganglion A-afferent population might be avoided by introducing it initially with a qualifier such as "nodosal." We chose to maintain the A-B designators because the A-B concept presented in the target article does not differ fundamentally from the one established decades ago.

Laughton contends that the problem we address is one of finding a name for a group of sensory neurons. On the contrary, we submit that there is no shortage of names but a lack of consensus on the distinct or congruent concepts they represent. We respect Laughton's nominalism in stating that "the ANS is ultimately whatever we say it is" but we disagree that the issue of classification is best resolved by ignoring it or by using arbitrary names. Operational definitions not grounded in structural patterns, natural taxonomies, or meaningful biological boundaries tend to have short half-lives in the sciences. In fact: We took away another moral from Lewis Carroll: Humpty Dumpty defined "glory" as a "nice-knock-down argument," but we don't know of any evidence that his capricious terminology took hold.

2. Drawing the boundaries

All systematists agree that the more traits used the more predictive the classification, and most acknowledge the value of weighting traits a posteriori. We have given heaviest weight to ontogenetic traits because these reflect the processes by which the different phenotypic patterns are generated. Despite our confidence in the predictiveness of ontogeny, choosing a trait is not without risk because the ontogenetic variable most important in determining phenotype may still be unknown to us. Moreover, the little quantitative embryological information available does not allow a precise correlation between embryonic traits and those of the adult stage. Nevertheless, a key part of our hypothesis is that the B-neuron traits discussed below will be congruent with the ontogenetic definition of the B-neuron population.

2.1. Some misunderstandings. The traditional systems we criticized attempted to classify virtually all components of the peripheral nervous system. This, together with broad generalizations we made about homeostasis, may have lead many commentators (**Andrews & Lawes, Davison & Sharkey, Grundy, Hsiao, Neuhuber, Ritter & Ritter**) to expect a system that would include more or even all afferent populations, and, in particular, those of the nodose ganglion. In arguing that B-neurons represented an autonomic afferent category, we did not mean to argue that they formed a closed, complete, and exclusive set, but our cognizance of the salient differences between B-neurons and placode-derived afferents (some referred to below) made us conclude that we lacked the necessary data to propose a more comprehensive taxonomy. We expressed our caveats in a footnote (cf. footnote 3, target article), but, with hindsight, we should have made our reservations more explicit. The commentaries of Grundy, Davison & Sharkey, and Ritter & Ritter

have listed some of these differences. In addition, capsaicin sensitivity discriminates nodosal and root-ganglion afferents too: In adult rats the former are more sensitive to the neurodegenerative actions (Jancsó et al. 1987). Finally, there has also been a functional dichotomy between spinal and nodosal visceral afferents regarding nociception (see Cervero 1985).

Thus we did not mean to imply that the A-B dichotomy accounts for all primary sensory neurons or that the B-neuron population holds a monopoly on autonomic or homeostatic functions. Perhaps some or all of the placodal visceral afferents can be considered part of a parallel but distinct class of sensory neurons, or they, in combination with the B-neurons, may be part of a still more fundamental division, as **Ritter & Ritter** suggest. One concern we share that was implicit in some of commentaries is that we cannot fully evaluate this B-neuron grouping until we examine it in the context of the more complete classification of the peripheral nervous system.

Because we have omitted nodosal afferents, some commentators (**Andrews & Lawes, Grundy,** and **Hsiao**) have questioned whether or not we can really consider B-neurons a *fundamental* division. The vagus is a large nerve, and as Hsiao indicates, it is commonly considered at least 90% afferent. We have recently determined that 70% is a more accurate figure (Prechtl & Powley 1990) for the rat, but by any estimate the nodose ganglion would have no more than 30,000 neurons; whereas only three of the lumbar ganglia (L4, L5, L6) contain about 20,000 B-neurons (estimated from data of Schmalbruch 1987).

Different types of visceral afferents with A-beta fibers were cited by **Neuhuber** with the suggestion that they represent exceptions to one of our generalizations. We did not propose that the B-population included all visceral afferents. Most spinal visceral afferents are B-neurons, but as expressed in the target article, the A-B classification is based on neuron type rather than innervation territory. We accordingly excluded from the B-neuron class, because of their distinctive fiber and receptor types, the well-known visceral afferents that innervate the mesentery of the cat. If the visceral afferents with A-beta fibers are found to be similar to B-neurons in most other respects, our generalization about fiber type (conduction velocity) should be reexamined; from what is currently known we would not lump them with B- or A-neurons.

2.2. Does RT97 label only A-neurons? In morphological (Price 1985, *rat;* Sommer et al. 1985, *mouse*) and developmental studies (Fontaine-Perus et al. 1985, *chick embryo*), it was concluded that substance P-like immunoreactivity was restricted to the B-neuron populations. The recent result cited by **Lawson** (McCarthy & Lawson 1989) that RT-97 labels some neurons that are substance P-like immunoreactive suggests to us that RT-97 labels not only A-neurons but also the minority of B-neurons that are thinly myelinated (see Andres 1961, *rat*). We consider these A-delta fibered cells B-neurons because apart from their myelination they have little in common with A-neurons; rather, like unmyelinated B-neurons, they are variously thermoceptive, nociceptive and/or capsaicin-sensitive. Those examined electrophysiologically are characterized by broad somatic spikes (see **Mendell**). They also show anatomic parallels central to the ganglion and in peripheral nerves. (We disagree with **Felten & Felten** about the myelinated fibers of the bone marrow [Lichtman 1981]: Because their diameters range from 1–5μm [Calvo & Forteza-Vila 1970] we believe that they are the A-delta fibers of B-neurons.) As indicated in the target article, we are open to the idea of intermediate populations; if the neurons positive for both substance *P* and RT-97 distinguish themselves on other features they should be considered separately. As Lawson uses the RT-97 marker in combination with other variables it is an effective discriminator for most A-neurons but we now doubt it is a monothetic trait. For perspective, however, it is worth remembering that neither acetylcholine nor noradrenaline represent monothetic traits for the autonomic divisions.

2.3. Capsaicin sensitivities. It is implied by **Jancsó** and **Szolcsányi** that the more fundamental neuronal grouping that approximates the B-neuron population is one based on capsaicin-sensitivity. **Maggi** elaborates on the subpopulations of B-neurons that could be defined on the basis of responsiveness to different capsaicin treatments. As Maggi points out, neonatal capsaicin in high doses in rats (see Nagy et al. 1983) affects most of the B-neuron population, including some thinly myelinated fibers. Although most of the results on capsaicin do not generalize to birds (Geisthövel et al. 1986, *duck;* Jancsó et al. 1985, *chicken*), perhaps a related trait in birds would identify an equivalent population. The discovery and characterization of different kinds of capsaicin-sensitive afferents has been, and is, an exciting development. The B-neuron concept preserves or even amplifies the functional similarities (see Lembeck 1987) of these afferents, regardless of whether they innervate deep or superficial tissues, or have C- or A-fibers. The only population of neurons for which the A-B and capsaicin-based classifications are not congruent is the capsaicin-sensitive neurons, which are placodally derived and project to the nucleus of the solitary tract and area postrema; as mentioned above (section 2.1), for the purposes of the general classification we think they differ enough to be considered separately.

2.4. Electrophysiological traits. Results are summarized by **Mendell** indicating that primary sensory neurons can be sorted on the basis of whether or not they show either broad somatic (i.e., neuronal soma) spikes with humps or narrow spikes. In the dorsal root ganglia, the populations with narrow or broad spikes so far delineated correspond to the A- and B-populations of the target article, except for a group of high-threshold afferents that have both broad spikes and A-beta type fibers (Koerber et al. 1988, *cat;* see also Harper & Lawson 1985, *rat*). It will be interesting to see whether all thermoreceptive afferents also show broad spikes. A classification will only be as good as the number of traits it considers and the ones raised by Mendell appear to be particularly important. Unlike ideas about function which are difficult to compare, a cellular physiological property is more tangible and can often be linked with a specific molecule (e.g., channel protein). So far we are impressed with the generalizing power of this physiological trait (broad spike) and would not rule out Mendell's suggestion that it, or a related correlate, might ultimately provide the most insightful classification.

2.5. Functional boundaries. Two functional issues are at hand: (1) The first concerns whether or not function should be used as the main criterion for delimiting neuron populations such as the B-afferents. (2) The second concerns the functional relations hypothesized between B-afferents and motor neurons, as discussed in section 3.

Most of us are interested in function; probably a number of the commentators would agree with Herrick's (1903) dictum that "The anatomical fact is dead and inert unless it is vivified not only by the salt of morphological ideas, but also by the fresh warm blood of functional explanations." **Engel,** however, questions the usefulness of structural observations altogether, or finds no merit in their correlation with function. Furthermore, **Haring** prefers a functional classification partly because its validity does not depend on phylogenetic, ontogenetic, and phenotypic considerations. We feel that attention to function alone is not likely to produce a predictive classification. One is reminded of the problematic and controversial attempts in biology to argue for homology on the basis of function (cf. Lorenz 1958). For example, the flying of birds and bats appears similar in function but an examination of the differences based on underlying wing structure predicts a wealth of other differences.

In our view, structural correlates provide a means of evaluating ideas about functional organization. Perhaps it is the abstract nature of function that makes it both appealing and troublesome as a classification criterion; it is much easier to agree on the size of a cell and its physiology than on its function. **Wall,** for example, claims that we failed to recognize some of the important functions of B-neurons. **Felten & Felten** think we have created an "artificial efferent category" (homeostatic). But even if we all subscribe in the same way to some standard list of functions (chemoreceptive, nociceptive, immunologic, trophic, exteroceptive, and so forth), will the neurons sort parsimoniously into such categories? The functional classifications suggested by **Haring** and by **Andrews & Lawes** may be indispensable for some heuristic purposes, but if one needs to organize most of the different kinds of facts (structure, physiology, pharmacology, pathophysiology) about a neuron population, we wager that the more tangible criteria are more trustworthy.

We also respect **Felten & Felten**'s proposal to lump afferents together with "other cells whose signal molecules reach the CNS and evoke somatic, autonomic, or neuroendocrine responses." (Taken literally, this might include endocrine cells like those of the adrenal medulla with afferents). But without converging evidence based on tangible cell traits, the "mobile afferents" concept may represent yet another special purpose classification based on a reasonable idea about function but not generalizable to other features. Felten & Felten's observation that lymphocytes can synthesize and secrete classical neuropeptides, however, is a piece of evidence in our view.

2.6. Other criteria. The BBS commentary format has been useful as a forum for introducing classification criteria that we did not incorporate in the target article. **Lembeck & Bucsics** have provided a systematic list of sensory neuron traits that should be considered in any wiser and more global classifications in the future. Data should also be incorporated from the work of Dodd and Jessell (1985; 1986) and colleagues on carbohydrate differentiation antigens; these antigens may play a role in determining the connectivity of primary sensory neurons. **Zilov** indicates that our survey failed to include the work of Soviet scientists in this area. We regret not being sufficiently aware of relevant findings available in the Russian literature but look forward to facilitated exchanges with our Soviet colleagues. We hope that Soviet authors and all others with critical contributions on this issue will use BBS's "Continuing Commentary" section to make their case known. Finally, **Wall** alluded to other seemingly important results that we neglected; the specifics were not provided, however, and hence their relevance is unclear to us.

3. Are B-neurons equipotent in autonomic and skeletomotor reflexes?

We are impressed by the structural and developmental similarities between autonomic and B-neurons and have difficulty thinking of the sensory-efferent functions of some B-neurons as anything but autonomic. From the commentaries, however, it must be concluded that the data we presented as evidence of a functional relationship between autonomic and B-neurons (section 4, "Functional ties. . .") were not convincing to all.

Our suggestion that nociceptive reflexes "are simply one of a variety of autonomic reflex types" may have been taken by some commentators as an overstatement. We did downplay the skeletomotor aspects of these reflexes (as rightly pointed out by **Cervero** and **Neuhuber**) because we wanted to encourage readers to think of nociceptive B-neurons in another way. The autonomic component of nociception is often considered (at least by the nonspecialist) as something secondary to the perception and visible motor reaction of pain. We hypothesize that in most ways the autonomic component is primary. For us the fact that sympathetic neurons (and not skeletomotor neurons) are intimately involved in a number of disorders of nociception is no accident but evidence of an underlying relationship. Although some kinds of cutaneous pain are attenuated by sympathectomy, we know of none that are altered by the denervation of striated muscle. Moreover, the diseases in which capsaicin-sensitive B-neurons are implicated involve ANS effectors (e.g., vasculature, bronchioles, bladder, see Maggi & Meli 1988) rather than skeletal muscles. In addition, as mentioned above, the physiological responses mediated directly by the axon reflexes in the centrifugally directed B-neuron processes are certainly more similar to autonomic responses than they are to skeletal responses. We acknowledge that these kinds of correlations are only qualitative, but it is also unsatisfactory to dismiss hastily all the similarities between autonomic and B-neurons without any effort to explain them.

Although we hypothesize that B-neurons are more closely related to the ANS than to other motor neurons, we also agree with **Felten & Felten** that logically afferents need not be defined in terms of a particular motor system. We think the B-neuron classification (hypothesis 1) can stand by itself without reference to a motor system. We have hence always used the term "B-afferents" and avoided the term "autonomic afferents" except for introducing the issue from Langley's perspective. The term "auto-

nomic afferents" could unnecessarily suggest that these afferents evolved secondary to the autonomic line; the obverse is also conceivable. We would also stress, however, that the idea of linking afferents to a motor system is not peculiar to our proposed classification. The widely adopted uses of the concept of "sympathetic afferents" and "parasympathetic afferents" is evidence that many authors recognize similar kinds of linkages.

Jancsó and **Lawson** fault us for not setting specific criteria for afferents involved in autonomic function. We may not have been explicit, but in section 4 of the target article we argued that B-neurons are more closely related to autonomic neurons (i.e., hypothesis 2) because they are more directly involved in autonomic functions and reflexes than in skeletomotor reflexes. Despite the persistent tendency to equate "visceral" with autonomic, we have, like most authors after Langley (1900), considered autonomic effector tissues to include virtually all those that are not striated muscles. As **Kobayashi** indicates, the terminal innervation by the ANS is often diffuse and without synaptic contacts. Moreover, some ANS effectors are not innervated but are influenced by neuroendocrine mechanisms. We accordingly viewed neurogenic inflammation as an autonomic function regardless of whether it occurred in the cutaneous, deep, or visceral tissues. For decades, other authors have also considered the neural mediation of immunologic reflexes to be autonomic (see Kuntz 1953) despite an incomplete understanding of the target tissues and the neural/neuroendocrine mechanisms. Nevertheless, we do acknowledge with **Haring** that on some of the finer points a generally accepted definition of the ANS is still lacking.

A final point relevant to our hypothesis that the ANS is the motor system most closely related to the B-neuron system. Some certainly thought our question was moot, but none of the commentaries explicitly argued that the B-neuron group or any subpopulation thereof was more closely related to another motor system on the basis of the criteria of ontogeny, cell phenotype, and function that we examined.

As examples of data inconsistent with our hypothesis 2, **Jancsó, Neuhuber,** and **Szolcsányi** cite the systematic investigations of Sato and Schmidt and colleagues (reviewed in Sato & Schmidt 1973; 1987) on electrical stimulation of somatic and visceral nerves, mostly in cats. In general, we think the nerve stimulation data are consistent with the A-B classification in that stimulation of afferent groups III and IV (B-neurons) always produces strong autonomic discharges and stimulation group I (A-neurons) never does. The finding that group II fibers (A-neurons) of cutaneous nerves also produce an ANS discharge is not predicted by the classification. Could these be the same feline afferents with A-beta fibers that **Mendell** identifies as having broad somatic spikes?

3.1. The hierarchy argument. Many commentators (**Andrews & Lawes, Felten & Felten, Grundy, Mendell, Yox**) emphasize that central nervous reflexes involve both autonomic and skeletomotor components. Of course, it is a given that the ANS is integrative, and in the target article we did not propose that B-neurons were exclusively involved in ANS functions. Instead, we offered an argument based on hierarchy that B-neurons are more directly or intimately involved in ANS than skeletomotor function. For example, Grundy refers to the vomiting reflex as "somatic," and Andrews & Lawes point out that it involves both autonomic and skeletomotor components; however, the fact that it can be achieved by the ANS alone (Johnson and Spalding 1974, *human*) suggests to us a more fundamental role for the ANS. Consistent with the hierarchy argument is **Szolcsányi**'s conclusion that with threshold stimulation, capsaicin-sensitive B-afferents participate in the regulation of cutaneous microcirculation, whereas nocifensive reflexes (including skeletomotor) require suprathreshold stimulation.

As indicated in the target article and reiterated by **Haring** and **Laughton:** Not all B-neurons contain substance *P* or are capsaicin-sensitive. Furthermore, we did not methodically examine for a hierarchical structure in the reflexes of other B-neurons. Such an argument could conceivably be made for thermoreceptive reflexes in mammals; for example, shivering (skeletomotor) occurs at a higher threshold than cutaneous vasoconstriction. Whether or not a similar argument would hold for other vertebrates is unclear. Furthermore, although we are unaware of the function of the innocuous mechanoreceptive afferents that we have included in the B-neuron population because of their C-fibers, we did not mean to imply, as **Ritter & Ritter** interpret, that these mechanoreceptive afferents are not involved in autonomic responses. Indeed, it would be to the credit of the A-B classification if such were found to be the case. We expect that new data and insights will clarify whether or not B-neurons are truly neutral in their functional alliances.

Cervero cites a result that cannot be dismissed with a hierarchy argument: Physiological stimulation of Pacinian corpuscles innervated by A-beta fibers elicits a greater sudomotor response than nociceptive stimulation (see Jänig 1985). This interesting "vibration reflex" may represent a specialization of cats; it is restricted to the hairless skin of the paw where it is thought to be useful for keeping the paw soft and flexible (Jänig 1985). The B-neuron proposal is based on a constellation of traits and considerations and is difficult to defend against argument by casual example: nevertheless, legitimate inconsistencies have been pointed out and should be tallied.

3.2. Higher nervous functions. Whereas we have concentrated on dissecting the functional roles of A- and B-neurons, **Hsiao** and **Yox** have elaborated on the integrative aspects of different afferent groups in the control of behavior. Different subpopulations of A- and B-neurons also participate jointly in higher functions of perception and behavior. Indeed, the gate control theory of pain (Melzack & Wall 1965), which has been so useful both clinically and theoretically, is based on an interaction of large- and small-fibered afferents, which appear to correspond to members of A- and B-populations, respectively.

Oehme, Krause & Hecht conclude that their results of the past two decades indicate a role for peripheral substance P in the feedback control of vegetative functions. The regulatory effects reported certainly could be attributed to substance P-containing B-neurons. Moreover, Oehme et al. hypothesize that substance P plays a normalizing role in the stress response and that their results are in good agreement with Lembeck's (1987) hypothesis that capsaicin-sensitive neurons constitute a "network of defense." This conclusion does not address

our hypotheses directly, however, in that it supports the functional unity of substance P-containing somatic and visceral B-neurons, it is consistent with the B-neuron grouping. One important theme raised by Oehme et al. and by **Lembeck & Bucsics** that we did not address is the involvement of B-afferents in neuroendocrine mechanisms.

4. An ontogeny reminiscent of phylogeny?

The A-B distinction interested us because it applied to a wide range of vertebrates and because certain features of the two cell types appeared to reflect a difference in phylogenetic histories. A key feature was the distinctive ontogenies of the two populations. **Wall** rejected our ontogenetic argument on the grounds that it was yet another version of the "ontogeny recapitulates phylogeny story." But as **Neuhuber** points out to the contrary, the inference we make is the opposite of what the "recapitulationist" would predict: We hypothesize that the late-born neurons have the more primitive or ancestral traits. Although contemporary systematists do not support recapitulationism per se, many subscribe to the idea akin to von Baer's law (see Gould 1977) that in development the more general and therefore more primitive characters appear earlier than the more particular ones. This rule is usually used to decide whether the presence or absence of a character among closely related taxa is primitive or uniquely derived and as such it may not apply to our discussion. Nevertheless, in accordance with that rule it is conceivable that the sequence of processes that leads to an earlier birth in A-neurons actually begins later than that of B-neurons. **Mendell**'s observation that the electrophysiological sequence whereby broad spikes with humps characterize the general and immature state after which A-neurons develop narrow spikes is consistent with our hypothesis. As discussed in the target article, the less-differentiated state of B-neurons is also suggested by their free nerve endings and slow conduction velocity; a discussion of these traits and of the evolution of the nervous system can be found in Ariëns Kappers et al. (1967). Interestingly enough, many B-neurons with their sensory-efferent functions (see **Jancsó, Maggi,** and **Szolcsányi**) are reminiscent of the ancestral "sensorimotor" neuron hypothesized by Parker (1919).

4.1. Primitive but not crude. We salute **Andrews & Lawes** for coming into the water with us and speculating on the neglected issue of the evolution of adaptive reflexes. Andrews & Lawes raise the important point that some of the B-neuron reflexes were acquired late in phylogeny. Indeed, many of the regulatory/preparatory reflexes of the mammalian ANS are not found in other taxa. Moreover, in many vertebrates the most important responses to adverse temperatures are behavioral. This does not necessarily mean, however, that all such reflexes emerged only after behavior with its highly integrative nervous system. We doubt that the requisite data for a satisfactory answer on this issue exist. Also, depending on how we define "autonomic" and "skeletomotor," different versions of the two positions are possible. In light of the considerations given in the previous paragraph, however, we do find it difficult to accept the idea that the reflex system involving the A-neurons is the more primitive. We expect that this interesting issue will be resolved by new contributions and interpretations.

Zilov and **Wall** have taken issue with our description of the hypothetical ancestor of the vertebrates as passive. Romer (1970) certainly did hypothesize a passive, sessile ancestor (see also Romer 1972). By "active" we mean that teleceptive senses are used in coordination with motor behaviors to localize and approach or avoid distant stimulus sources. The "passive" animal, on the other hand, does not locate and approach; rather, it floats about while sampling nutrients that fall into its cilia. Nutrients are accepted by the cilia beating in the direction of an orifice and rejected by beating in the opposite direction. Contrary to Zilov's interpretation, we did not try to raise the issue of "endogenous and exogenous factors," as discussed in Marler & Hamilton (1966; p. 9).

Conclusion

What does the ledger on B-neuron classification look like then? On balance, we would reaffirm our rhetorical remark from the target article: We think Langley, if he had had access to today's data, including the additional complexities reviewed in the commentaries, would have assigned B-neurons to the autonomic afferent category he left empty. A physiologist who valued morphological and histochemical data, however, Langley might not receive a sympathetic audience with some of our commentators. Regardless of Langley's inclinations, it is clear from the commentaries as well as from the figures and tables of the target article that the neurosciences are collecting more facts than concepts to accommodate them. For the last few decades, the A-B neuron distinction has served only in a specialized role for neurocytologists. More recently it has gained importance among histochemists, pharmacologists, and embryologists. We think the time is ripe to further test the generality of this concept. Although all of us split hairs on the basis of mammalian data, the A-B classification was intended to generalize beyond rats and cats. As such, the concept will have to adopt the kind of coarse boundaries that accommodate, as well as highlight, interspecific differences. Nonetheless, a few of the crisp lines we drew between A- and B-neurons have been blurred by additional data and considerations raised by the commentators; the distinctions we made deserve further investigation and discussion. For example, the margin of overlap we proposed between fast- and slow-conducting fibers in the A-delta range might need broadening to include some A-beta fibers, at least in the case of cats. Although the B-neuron definition in the target article and similar concepts of some commentators differed only by small percentages of afferents, the various boundaries proposed should be further compared in the context of new observations on other traits.

Our proposal that B-neurons are more closely related to the ANS is more novel and goes against the grain of long-established ideas about function and sensation. It will be tested as we gain more detailed knowledge of connections and reflex hierarchies of sensory neurons. Although the commentaries have focused on a number of problematic aspects of drawing a connection between any afferent group and the ANS, the similarities between

autonomic and B-neuron populations are too numerous to be explained by chance alone, and no alternative to our explanation of this correlation has been offered. If it is recognized that the ANS is a complex and richly diverse system that cannot be understood through a simple invariant list of traits, we think the case for an association of B-neurons with autonomic neurons is particularly strong.

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Letters "a" and "r" appearing before authors' initials refer to target article and response respectively.

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